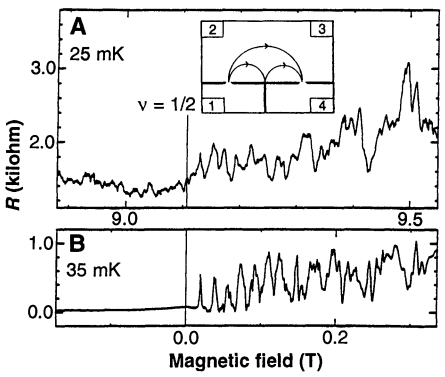

Fig. 4. The resistance $R = V_{34}/I_{21}$ for the magnetic focusing sample shown in the inset. (**A**) Focusing peaks of electrons near $B = 0$, and (**B**) focusing peaks of composite fermions near $B^* = 0$ (that is, near $\nu = 1/2$). The scales of B and B^* differ by a factor of about $\sqrt{2}$. A qualitative difference between the positive and negative B^* (that is, between $\nu > 1/2$ and $\nu < 1/2$) is evident, as is the one-to-one correspondence between several composite fermion and electron focusing peaks. [Reprinted from (*30*) with permission of Goldman *et al.*]

the lattice; some of the most relevant commensurate orbits are shown in the figure. Similar dimensional resonances of composite fermions show up near $B^* = 0$. Goldman *et al.* (*30*) observed magnetic focusing of composite fermions near $\nu = 1/2$. The experimental setup is shown in Fig. 4.; the current flows from 1 to 2, and the voltage is measured between 3 and 4. Near $B = 0$, a number of quasi-periodic peaks are observed (Fig. 4B), which occur at those values of B where the electrons coming straight out of the left constriction are focused into the right constriction, possibly after several specular reflections from the gate. Similar quasi-periodic structure was observed near $B^* = 0$ (Fig. 4A). The close correspondence between the electron and the composite fermion peaks is evident in both Figs. 3 and 4. These experiments confirm the existence of composite fermions in the compressible region near $\nu = 1/2$ by demonstrating that the dynamics of the charge carriers are described by the effective field B^* rather than the external field B. Thus, the composite fermion framework has not only provided a simple "one-step" explanation of the FQHE, it has also helped reveal the nontrivial nature of the metallic state at even-denominator fractions.

Conclusion

The following picture has finally emerged. First, electrons form LLs because of quantization of their kinetic energy. This results in the IQHE. Within the lowest LL, in a range of filling factor, electrons minimize their interaction energy by capturing vortices and transforming into composite fermions. Even though the composite fermions are quantum mechanical particles with a true many-body character, they may be treated, for most purposes, as ordinary noninteracting fermions moving in an effective magnetic field. They form quasi-LLs, execute cyclotron motion, and fill a Fermi sea. The formation of composite fermions lies at the root of the FQHE and several other fascinating experimental phenomena.

REFERENCES AND NOTES

1. E. H. Hall, *Am. J. Math* **2**, 287 (1879).
2. K. von Klitzing, G. Dorda, M. Pepper, *Phys. Rev. Lett.* **45**, 494 (1980).
3. D. C. Tsui *et al.*, *ibid.* **48**, 1559 (1982).
4. See L. D. Landau and E. M. Lifshitz, *Quantum Mechanics* (Addison-Wesley, Reading, MA, 1965), pp. 424–426.
5. R. B. Laughlin, *Phys. Rev. B* **23**, 5632 (1981).
6. ———, *Phys. Rev. Lett.* **50**, 1395 (1983).
7. For example, G. Fano, F. Ortolani, E. Colombo, *Phys. Rev. B* **34**, 2670 (1986); F. D. M. Haldane and E. H. Rezayi, *Phys. Rev. Lett.* **54**, 237 (1985).
8. F. D. M. Haldane, *Phys. Rev. Lett.* **51**, 605 (1983).
9. B. I. Halperin, *ibid.* **52**, 1583 (1984).
10. See J. K. Jain, *Adv. Phys.* **41**, 105 (1992).
11. S. M. Girvin and A. H. MacDonald, *Phys. Rev. Lett.* **58**, 1252 (1987).
12. S. C. Zhang *et al.*, *ibid.* **62**, 82 (1989).
13. N. Read, *ibid.*, p. 86.
14. J. K. Jain, *ibid.* **63**, 199 (1989).
15. To see how multiplication by the Jastrow factor attaches $2m$ vortices to each electron, fix all z_j in the Jastrow factor except z_1. As z_1 traverses in a closed loop around any other electron, it acquires a phase of $4m\pi$, that is, it sees $2m$ vortices on all other electrons.
16. N. Trivedi and J. K. Jain, *Mod. Phys. Lett. B* **5**, 503 (1991).
17. G. Dev and J. K. Jain, *Phys. Rev. Lett.* **69**, 2843 (1992).
18. X. G. Wu, G. Dev, J. K. Jain, *ibid.* **71**, 153 (1993); X. G. Wu and J. K. Jain, preprint.
19. E. H. Rezayi and A. H. MacDonald, *Phys. Rev. B* **44**, 8395 (1991); M. Kasner and W. Apel, *ibid.* **48**, 11435 (1993); E. H. Rezayi and N. Read, *Phys. Rev. Lett.* **72**, 900 (1994).
20. V. J. Goldman *et al.*, *Phys. Rev. Lett.* **65**, 907 (1990).
21. J. K. Jain, S. A. Kivelson, N. Trivedi, *ibid.* **64**, 1297 (1990).
22. B. I. Halperin, P. A. Lee, N. Read, *Phys. Rev. B* **47**, 7312 (1993).
23. R. R. Du *et al.*, *Phys. Rev. Lett.* **70**, 2944 (1993).
24. Also see, I. V. Kukushkin, R. J. Haug, K. von Klitzing, K. Ploog, *ibid.* **72**, 736 (1994).
25. D. R. Leadley *et al.*, *ibid.*, p. 1906.
26. R. R. Du, H. L. Stormer, D. C. Tsui, L. N. Pfeiffer, K. W. West, *Solid State Commun.* **90**, 71 (1994).
27. H. W. Jiang, H. L. Stormer, D. C. Tsui, L. N. Pfeiffer, K. W. West, *Phys. Rev. B* **40**, 12013 (1989); R. L. Willett *et al.*, *Phys. Rev. Lett.* **65**, 112 (1990).
28. R. L. Willett, R. R. Ruel, K. W. West, L. N. Pfeiffer, *Phys. Rev. Lett.* **71**, 3846 (1993).
29. W. Kang *et al.*, *ibid.*, p. 3850.
30. V. J. Goldman *et al.*, *ibid.* **72**, 2065 (1994).
31. V. J. Goldman, unpublished figure.

32. Financial support from the National Science Foundation under grant DMR93-18739 is acknowledged.

The Sverdlovsk Anthrax Outbreak of 1979

Matthew Meselson,* Jeanne Guillemin, Martin Hugh-Jones, Alexander Langmuir,† Ilona Popova, Alexis Shelokov, Olga Yampolskaya

In April and May 1979, an unusual anthrax epidemic occurred in Sverdlovsk, Union of Soviet Socialist Republics. Soviet officials attributed it to consumption of contaminated meat. U.S. agencies attributed it to inhalation of spores accidentally released at a military microbiology facility in the city. Epidemiological data show that most victims worked or lived in a narrow zone extending from the military facility to the southern city limit. Farther south, livestock died of anthrax along the zone's extended axis. The zone paralleled the northerly wind that prevailed shortly before the outbreak. It is concluded that the escape of an aerosol of anthrax pathogen at the military facility caused the outbreak.

Anthrax is an acute disease that primarily affects domesticated and wild herbivores and is caused by the spore-forming bacterium *Bacillus anthracis*. Human anthrax results from cutaneous infection or, more rarely, from ingestion or inhalation of the pathogen from contaminated animal products (*1*). Anthrax has also caused concern as a possible agent of biological warfare (*2*).

Early in 1980, reports appeared in the Western press of an anthrax epidemic in Sverdlovsk, a city of 1.2 million people 1400 km east of Moscow (*3*, *4*). Later that year, articles in Soviet medical, veterinary, and legal journals reported an anthrax outbreak among livestock south of the city in the spring of 1979 and stated that people developed gastrointestinal anthrax after eating contaminated meat and cutaneous anthrax after contact with diseased animals (*5*–*7*). The epidemic has occasioned intense international debate and speculation as to whether it was natural or accidental and, if accidental, whether it resulted from activities prohibited by the Biological Weapons Convention of 1972 (*8*).

In 1986, one of the present authors (M.M.) renewed previously unsuccessful re-

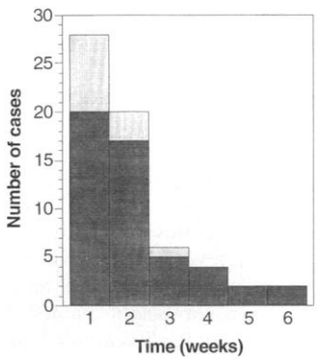

Fig. 1. Time course of the epidemic: onsets of fatal cases by week. The first week begins on 4 April 1979, the date of the first onset we recorded. Lighter shading represents cases for which the onset date is unknown and is estimated by subtracting 3 days from the date of death.

quests to Soviet officials to bring independent scientists to Sverdlovsk to investigate. This resulted in an invitation to come to Moscow for discussions with four physicians who had gone to Sverdlovsk to deal with the outbreak (including another of the present authors, O.Y., who was a clinician in the intensive care unit set aside to treat the victims). In 1988, two of these Soviet physicians visited the United States, where they gave formal presentations and participated in discussions with private and government specialists. According to their account, contaminated animals and meat from an epizootic south of the city starting in late March 1979 caused 96 cases of human anthrax with onsets from 4 April to 18 May. Of these cases, 79 were said to be gastrointestinal and 17 cutaneous, with 64 deaths among the former and none among the latter (9).

The impression left on those of the present authors who took part in the U.S. meetings (J.G., A.L., M.M., and A.S.) was that a plausible case had been made but that additional epidemiological and pathoanatomical evidence was needed. Further requests by M.M. for an invitation led to an on-site study in Sverdlovsk, initiated there in June 1992, and a return visit in August 1993.

Starting in 1990, several articles about the epidemic appeared in the Russian press (*10*). These included interviews with Sverdlovsk physicians who questioned the foodborne explanation of the epidemic and with officials at the military microbiology facility. These officials said that in 1979 they had been developing an improved vaccine against anthrax but knew of no escape of anthrax pathogen. Late in 1991, Russian President Boris Yeltsin, who in 1979 was the chief Communist Party official of the Sverdlovsk region, directed his Counsellor for Ecology and Health to determine the origin of the epidemic (*11*). In May 1992, Yeltsin was quoted as saying that "the KGB admitted that our military developments were the cause" (*12*). No further information was provided. Subsequently, the chairman of the committee created by Yeltsin to oversee biological and chemical disarmament expressed doubt that the infection originated at the military facility and stated that his committee would conduct its own investigation (*13*). The results of that investigation have not yet appeared.

Pathoanatomical evidence that the fatal cases were inhalatory, recently published by Russian pathologists who performed autopsies during the epidemic (*14–16*), is summarized in an earlier report from the present study (*17*). Here we report epidemiological findings that confirm that the pathogen was airborne, and we identify the location and date of its escape into the atmosphere.

Table 1. Case data. Case numbers for fatalities are as they appear on the administrative list. Case numbers for survivors are arbitrary. Days of onset and death are counted from 1 April 1979. Abbreviations: O, onset; D, death; R, residence; W, workplace; *, unidentified man; ?, not known; ma, mid-April; s, survivor; c, cutaneous survivor; +, in high-risk zone; −, outside high-risk zone; a, had two residences, one in Compound 32; p, pensioner; r, daytime military reservist at Compound 32; u, unemployed. Patients 25, 29, 48, and 87 were home on vacation during the first week of April.

Case no.	Age/sex	O/D	R/W	Case no.	Age/sex	O/D	R/W
*	?/m	?/?	?/?	51	31/m	10/15	−/?
32	40/m	?/?	−/?	40	37/m	12/15	+/+
67	26/m	?/?	+/+	36	68/f	?/16	a/p
68	32/f	?/?	+/+	35	52/m	13/16	+/+
8	60/f	?/8	+/+	34	43/m	14/16	−/+
18	38/m	6/8	−/?	38	69/f	14/16	+/p
16	40/m	?/9	+/+	39	49/m	14/16	+/+
66	55/f	?/9	−/?	41	41/f	?/17	+/p
1	44/m	6/9	+/+	42	43/m	15/18	−/+
2	46/m	6/9	+/+	43	39/m	15/19	+/u
5	66/m	7/9	−/+	44	47/m	15/21	−/?
49	51/m	8/9	+/+	45	45/m	?/22	+/+
21	49/m	?/10	−/?	46	39/m	20/23	−/+
4	54/f	5/10	+/+	47	41/m	21/24	−/−
6	40/m	7/10	−/?	52	42/m	21/24	−/−
20	39/m	7/10	−/−	53	47/m	22/24	−/−
17	67/f	8/10	+/+	48	57/f	15/25	+/−
9	72/f	9/10	+/p	54	50/f	17/25	−/?
7	52/f	?/11	+/+	55	31/m	23/25	+/+
19	64/f	?/11	−/?	57	31/m	27/28	−/r
22	27/m	?/11	+/+	58	32/m	29/30	−/+
23	43/m	?/11	−/r	59	55/m	27/31	−/+
3	48/f	4/11	−/+	60	33/m	25/33	−/r
10	27/m	9/11	+/−	61	42/m	34/40	−/+
65	72/m	9/11	+/p	62	29/m	39/40	+/+
15	48/f	6/12	+/+	63	25/m	37/42	−/+
25	46/m	10/12	−/−	64	28/m	42/46	−/?
12	38/m	11/12	−/+	90	28/m	?/s	−/+
11	27/m	12/12	−/r	82	68/f	13/s	+/+
26	67/m	9/13	+/p	80	49/m	14/c	+/−
13	24/f	10/13	+/+	84	55/f	ma/c	−/+
24	65/f	10/13	+/p	85	40/f	ma/s	+/+
28	47/m	11/13	+/+	89	50/f	34/s	+/−
14	49/m	12/13	−/+	86	28/m	37/s	−/−
27	64/m	10/14	+/+	81	29/m	38/s	+/+
31	42/m	11/14	−/r	83	45/m	41/s	+/+
30	52/m	12/14	+/+	87	41/m	42/s	+/−
29	45/m	13/14	+/+	88	37/m	45/s	+/+
50	72/f	?/15	+/p				

Sources of Information

Local medical officials told us that hospital and public health records of the epidemic had been confiscated by the KGB. We nevertheless were able to assemble detailed information on many patients from a variety of sources. (i) An administrative list giving names, birth years, and residence addresses of 68 people who died, compiled from KGB

M. Meselson is in the Department of Molecular and Cellular Biology, Harvard University, Cambridge, MA 02138, USA. J. Guillemin is in the Department of Sociology, Boston College, Chestnut Hill, MA 02167, USA. M. Hugh-Jones is in the School of Veterinary Medicine, Louisiana State University, Baton Rouge, LA 70803, USA. A. Langmuir is in the School of Hygiene and Public Health, Johns Hopkins University, Baltimore, MD 21205, USA. I. Popova is in the Social and Political Sciences Division, Ural State University, Ekaterinburg 620083, Russia. A. Shelokov is in the Government Services Division, Salk Institute, San Antonio, TX 78228, USA. O. Yampolskaya is in the Botkin Hospital, Moscow 125101, Russia.

*To whom correspondence should be addressed.
†Deceased 22 November 1993.

records and used by the Russian government to compensate families of the deceased (*18*). Comparison with other sources of information, including those listed below, indicates that the administrative list may include most or all of those who died of anthrax. (ii) Household interviews with relatives and friends of 43 people on the administrative list and with 9 survivors or their relatives (or both). The interviews (directed by J.G.) were designed to identify the workplaces and other whereabouts of patients before their illness. (iii) Grave markers, giving names and dates of birth and death, that we inspected in the cemetery sector set aside for the anthrax victims. These include 61 markers with names that are also on the administrative list and 5 with illegible or missing name plates. (iv) Pathologists' notes regarding 42 autopsies that resulted in a diagnosis of anthrax (*14–17*). All but 1 of the 42, an unidentified man, are on the administrative list. The notes include name, age, and dates of onset, admission, death, and autopsy. (v) Various hospital lists, with names, residence addresses, and, in some cases, workplaces or diagnoses (or both) of approximately 110 patients who were apparently screened for anthrax, 48 of whom are indicated to have died. Of the latter, 46 are on the administrative list. (vi) Full clinical case histories of 5 survivors hospitalized in May 1979.

Current street and regional maps were purchased in Sverdlovsk, which is known again by its prerevolutionary name of Ekaterinburg. The city is the seat of an administrative region, or *oblast*, named Sverdlovskaya. The city itself is divided among a number of districts, or *rayon*, the most southerly being Chkalovskiy *rayon*. A satellite photograph of the city taken 31 August 1988 was purchased from SPOT Image Corporation (Reston, Virginia). Archived meteorological data from the city's Koltsovo airport were obtained from the National Center for Atmospheric Research (Boulder, Colorado).

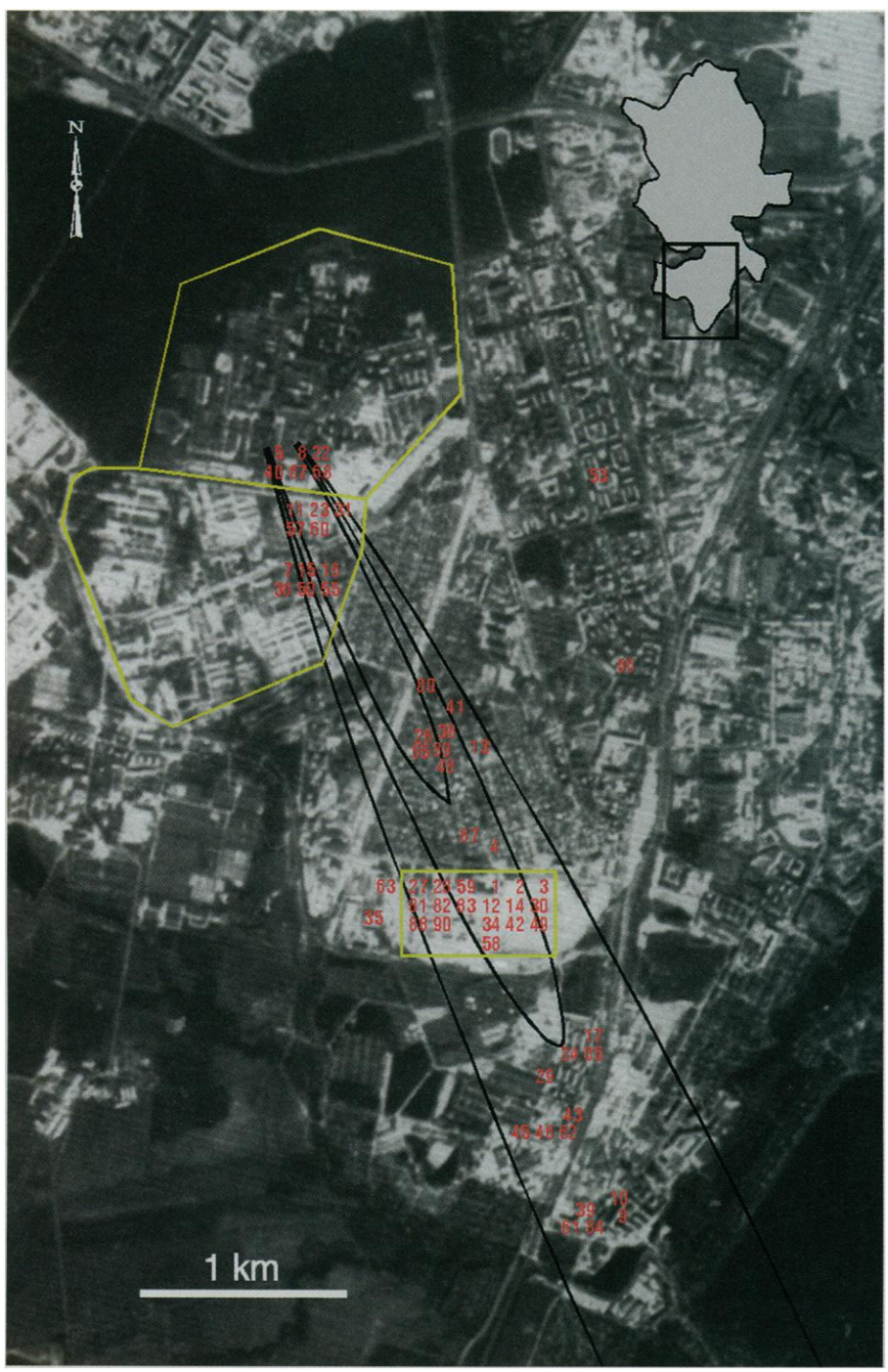

Fig. 2. Probable locations of patients when exposed. The part of the city shown in the photograph is enclosed by a rectangle in the inset. Case numbers, in red, correspond to those in Table 1 and indicate probable daytime locations of patients during the period 2 to 6 April 1979. Of the 66 patients mapped as explained in the text, 62 mapped in the area shown. This distribution may be somewhat biased against residence locations, because daytime workers not on vacation who both resided and worked in the high-risk zone are mapped at their workplaces. Proceeding from north to south, Compound 19, Compound 32, and the ceramics factory are outlined in yellow. The five patients residing in Compound 32 are mapped at their apartments. Within the compound, the placement of an additional, part-time resident and of the five reservists is arbitrary, as is that of the five residents and a nonresident employee in Compound 19. Patients known to have worked in the ceramics pipe shop are mapped in the eastern part of the factory area, where the pipe shop is located. Calculated contours of constant dosage are shown in black. Approximately 7000 people lived in the area bounded by the outermost contour of constant dosage, Compound 32, and the ceramics factory. The terrain slopes gently downward by about 40 m from Compound 19 to the ceramics factory.

Case Data

Table 1 presents information on 66 patients who died and 11 who survived. The fatalities include the unidentified man and all people named on the administrative list, except for three patients for whom recent reexamination of preserved autopsy specimens does not support a diagnosis of anthrax (*19*). For survivors, diagnoses of anthrax are supported by clinical case histories or hospital lists or both and by household interviews.

Overall, 55 of the 77 tabulated patients are men, whose mean age was 42. The mean

age for women was 55. No man was younger than 24, and only two women, aged 24 and 32, were under 40. Recorded onsets span a period of nearly 6 weeks, 4 April to 15 May, with a mean time between onset and death of 3 days (Table 1 and Fig. 1).

Approximately 60% of the 33 men for whom we have relevant information were described as moderate or heavy smokers and nearly half as moderate or heavy drinkers. None of the women was said to have smoked or to have consumed alcohol more than occasionally. Few patients were reported to have had serious preexisting medical conditions. Among the 35 men whose occupation in 1979 we could determine, the most common occupation was welder, accounting for 7.

In descending order of frequency, symptoms reported in household interviews included fever, dyspnea, cough, headache, vomiting, chills, weakness, abdominal pain, and chest pain. Two of the survivors interviewed reported having had cutaneous anthrax, one on the back of the neck, the other on the shoulder. Hospitalized patients were treated with penicillin, cephalosporin, chloramphenicol, anti-anthrax globulin, corticosteroids, osmoregulatory solutions, and artificial respiration. The average hospital stay was 1 to 2 days for fatal cases and approximately 3 weeks for survivors. To the best of our knowledge, no human anthrax has occurred in the Sverdlovsk region since 1979.

Public Health Response

Public health measures were initially directed by an emergency commission formed in Chkalovskiy *rayon*, where most patients lived and worked. On or about 10 April, overall direction was assumed by a commission that was constituted at *oblast* level and included the USSR Deputy Minister of Health. Military personnel participated little if at all in the implementation of medical and public health measures.

Before the bacteriological confirmation of anthrax, on 11 April (*14*), patients were taken to hospitals served by the ambulance or polyclinic of first contact. Starting on 12 April, most patients presenting with high fever or other indications of possible anthrax or who died at home or elsewhere of suspected anthrax were taken to city hospital No. 40, where separate areas were designated for screening suspect cases and for treating nonsystemic cutaneous cases, for intensive care, and for autopsy. Bodies of those who died were placed in coffins with chlorinated lime and buried in a single sector of a city cemetery. Medical and sanitation teams recruited from local hospitals and factories visited homes of suspected and confirmed cases throughout the city, where they conducted medical interviews, dispensed prophylactic tetracycline to patients' households, disinfected kitchens and sick rooms, and took meat and environmental samples for bacteriological testing. Human anthrax is not considered contagious, nor was there any evidence of person-to-person transmission. In the part of Chkalovskiy *rayon* where most patients resided, building exteriors and trees were washed by local fire brigades, stray dogs were shot by police, and several previously unpaved streets were asphalted. Newspaper articles and posters warned of the risk of anthrax from consumption of uninspected meat and contact with sick animals. Uninspected meat in vehicles entering the city from the south was confiscated and burned at highway checkpoints.

Starting in mid-April, a voluntary immunization program using a live nonencapsulated spore vaccine (designated STI) was carried out for healthy persons 18 to 55 years old served by clinics in Chkalovskiy *rayon*. Posters urged citizens to obtain "prophylactic immunization against anthrax" at designated times and places. Of the 59,000 people considered eligible, about 80% were vaccinated at least once.

Geographical Distribution of Human Cases

Most of the 77 tabulated patients lived and worked in the southern area of the city shown in Fig. 2. Of the 66 patients for whom we have both residence and workplace locations, 9 lived and regularly worked outside of this area. Interviews with relatives and friends revealed that five of these nine had attended military reserve classes during the first week of April 1979 at Compound 32, an army base in the affected area. Respondents stated and, in one case, showed diary notes establishing that the first day of attendance was Monday, 2 April, that classes began at 0830, and that participants returned home each evening. Assuming that the reservists were exposed while at or near Compound 32, this must have occurred during the daytime in the week of 2 April.

In order to locate the high-risk area more precisely, we prepared a map showing probable daytime locations of the 66 patients during the week of 2 April. Those with residence or work addresses in military compounds or attending reserve classes were placed in the appropriate military compound; night workers, pensioners, unemployed people, and vacationers were placed at their homes; and all other workers were placed at their workplaces. This mapped 57 patients in a narrow zone approximately 4 km long, extending from the military microbiology facility to the southern city limit. The remaining nine worked outside this zone, but three of them resided within it. Placing the latter at their residences gives the distribution shown in Fig. 2, with 60 of the 66 mapped cases in the

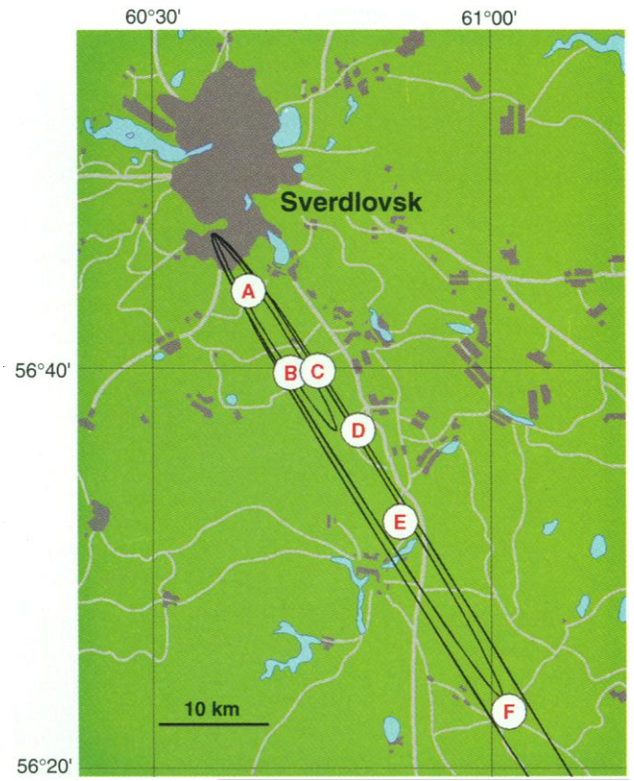

Fig. 3. Villages with animal anthrax. Six villages where livestock died of anthrax in April 1979 are A, Rudniy; B, Bolshoye Sedelnikovo; C, Maloye Sedelnikovo; D, Pervomaiskiy; E, Kashino; and F, Abramovo. Settled areas are shown in gray, roads in white, lakes in blue, and calculated contours of constant dosage in black.

high-risk zone, 2 cases east of it, and 4 cases north or east of the area of the figure. Of these six patients who both worked and lived outside the high-risk zone, three had occupations (truck driver, pipe layer, and telephone worker) that might have taken them there, one was temporarily working in Chkalovskiy *rayon*, one was on vacation, and inadequate information was available for another.

At the northern end of the high-risk zone is the military microbiology facility, Compound 19, followed to the south by Compound 32. Both compounds include numerous buildings, with four- and five-story apartment houses for about 5000 people at the former and 10,000 at the latter. The administrative list includes five people who lived in Compound 19 and five who lived in Compound 32. All of the latter resided in four adjacent apartment buildings in the eastern part of the compound. Interviews in Compound 32 indicated that all of its residents who died of anthrax are on the administrative list. Interviews were not conducted in Compound 19.

Adjacent to Compound 32 and extending south-southeast for about 1.5 km is a residential neighborhood with a 1979 population density of approximately 10,000 per square kilometer, composed of small single-story private houses and a few apartment houses, shops, and schools. Just south of this is a ceramics factory that had about 1500 daytime employees. Of the 18 tabulated patients who were employees there, 10 worked in a large unpartitioned building where ceramic pipe was made and which had a daytime work force of about 450. The attack rate at the ceramics factory therefore appears to be 1 to 2%. Still farther south are several smaller factories, apartment buildings, private houses, schools, and shops, beyond which begins open countryside with patches of woodland.

Animal Anthrax

Anthrax has been enzootic in Sverdlovskaya *oblast* since before the 1917 revolution (*20*). Local officials recalled an outbreak of anthrax among sheep and cattle south of the city in early spring 1979. A detailed report of a commission of veterinarians and local officials describes the epizootic in Abramovo, a village of approximately 100 houses 50 km south-southeast of Compound 19. The report, dated 25 April 1979, records the deaths or forced slaughter of seven sheep and a cow with anthrax that was confirmed by veterinary examination. The first such losses were of two sheep on 5 April, followed by two more on each of the next 2 days, another on 8 April, and a cow on 10 April, all belonging to different private owners. These losses were substantiated by interviews we conducted with owners of six of the sheep that died. Respondents said there had been no human anthrax in the village. During a livestock immunization program started on 10 April, 298 sheep were given anti-anthrax serum or vaccine or both. The attack rate among sheep at Abramovo therefore appears to have been approximately 2%.

In addition, we obtained veterinary reports of bacteriological tests positive for anthrax in samples from three sheep from three farms in the village of Kashino, one sheep from Pervomaisky, and a cow from Rudniy, the earliest samples being received for testing on 6 April. Although other documents cite the forced slaughter of a sheep in Rudniy on 28 March and the death of another in Abramovo on 3 April, the earliest livestock losses for which we have documentation of a diagnosis of anthrax are those in Abramovo on 5 April.

Altogether, Soviet publications (*6*, *7*) and the documents we obtained cite outbreaks of anthrax among livestock in six villages: Rudniy, Bolshoye Sedelnikovo, Maloye Sedelnikovo, Pervomaiskiy, Kashino, and Abramovo. All six villages lie along the extended axis of the high-risk zone of human anthrax (Fig. 3). The centerline of human and livestock cases has a compass bearing of 330° ± 10°.

Meteorology

Surface (10 m) observations reported at 3-hour intervals from Koltsovo airport, 10 km east of the ceramics factory, were examined in order to identify times when the wind direction was parallel to the centerline of human and animal cases. During the time that the reservists who contracted anthrax were at Compound 32, but before the first recorded human onsets, this occurred only on Monday, 2 April, when northerly winds from the sector 320° to 350° were reported throughout the period 0400 to 1900 local time (Fig. 4).

During the rest of April, winds from this sector seldom occurred, accounting for fewer than 2% of reports. During the period of northerly wind on 2 April, which followed the passage of a cold front, the wind speed was 4 to 6 m s^{-1}, the temperature −10° to −3°C, the relative humidity 50 to 66%, the sky cloudless, and the midday sun 39° above the horizon. These conditions of insolation and wind speed indicate that the atmosphere near the surface was of neutral stability (*21*). As is consistent with this, temperature measurements at 500 to 1000 m indicated a slightly stable atmosphere at 0400 and 1000 hours, becoming neutral by 1600.

Discussion

We have presented evidence that (i) most people who contracted anthrax worked, lived, or attended daytime military reserve classes during the first week of April 1979 in a narrow zone, with its northern end in a military microbiology facility in the city and its other end near the city limit 4 km to the south; (ii) livestock died of anthrax in villages located along the extended axis of this same zone, out to a distance of 50 km; (iii) a northerly wind parallel to the high-risk zone prevailed during most of the day on Monday, 2 April, the first day that the military reservists who contracted anthrax were within the zone; and (iv) the first cases of human and animal anthrax appeared 2 to 3 days thereafter.

We conclude that the outbreak resulted from the windborne spread of an aerosol of anthrax pathogen, that the source was at the military microbiology facility, and that the escape of pathogen occurred during the day on Monday, 2 April. The epidemic is the largest documented outbreak of human inhalation anthrax.

The narrowness of the zone of human and animal anthrax and the infrequency of northerly winds parallel to the zone after 2 April suggest that most or all infections resulted from the escape of anthrax pathogen on that day. Owing to the inefficiency of aerosol deposition and resuspension (*22*, *23*), few if any inhalatory infections are likely to have resulted from secondary aerosols on subsequent days. A single date of inhalatory infection is also consistent with the steady decline of onsets of fatal cases in

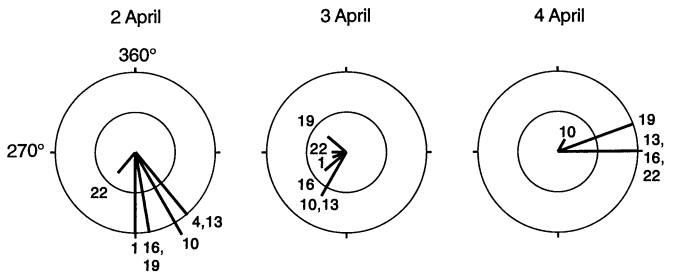

Fig. 4. Wind directions and speeds reported from Koltsovo airport for the period 2 to 4 April 1979. Numbers at the downwind end of each line are local standard times. Inner and outer concentric circles designate wind speeds of 2.5 and 5.0 m s^{-1}, respectively. Zero wind speed was reported for 0400 on 3 April and for 0100 and 0400 on 4 April. No data were reported for 0700.

successive weeks of the epidemic.

Accepting 2 April as the only date of inhalatory exposure, the longest incubation period for fatal cases was 43 days and the modal incubation period was 9 to 10 days. This is longer than the incubation period of 2 to 6 days that has been estimated from very limited data for humans (*24*). Experiments with nonhuman primates have shown, however, that anthrax spores can remain viable in the lungs for many weeks and that the average incubation period depends inversely on dose, with individual incubation periods ranging between 2 and approximately 90 days (*25*, *26*).

The absence of inhalation anthrax patients younger than 24 remains unexplained. Although nothing suggests a lack of children or young adults in Chkalovskiy *rayon* in 1979, they may have been underrepresented in the aerosol plume. Alternatively, older people may have been more susceptible, which may also explain the lack of young people in epidemics of inhalation anthrax early in this century in Russian rural communities (*27*).

It may be asked if the geographical distribution of cases is consistent with the distribution expected for an aerosol of anthrax spores released at Compound 19 under the daytime atmospheric conditions of 2 April 1979. Contours of constant dosage were calculated from a Gaussian plume model of atmospheric dispersion, with standard deviations given by Briggs for neutral atmospheric stability in open country (*21*), a wind speed of 5 m s^{-1}, a nominal release height of 10 m, and no limit to vertical mixing (Figs. 2 and 3). The aerosol is assumed to consist of particles of diameter <5 μm, as can be produced, for example, by a laboratory aerosol generator (*28*), and to have a negligible infectivity decay rate (<0.001 min^{-1}) (*2*) and a deposition velocity <0.5 cm s^{-1}, which is insufficient to cause appreciable reduction of dosage at downwind distances less than 50 km (*29*–*31*). Dosage contours are not shown closer than 300 m to the putative source, as the dosage at shorter distances depends sensitively on the effective release height of the aerosol and the configuration of nearby buildings.

People indoors will be exposed to the same total dosage as those outside if filtration, deposition, and infectivity decay of the aerosol are negligible. The negligibility of these factors is supported by the absence of significant dosage reduction in field studies of protection afforded by tightly constructed buildings against an outside spore aerosol (*32*).

The calculated contours of constant dosage, like the zone of high human and animal risk, are long and narrow. Contours are shown at 10, 5, and 1 × 10^{-8} *Q* spore minutes per cubic meter (Fig. 2) and at 0.5, 0.2, and 0.1 × 10^{-8} *Q* spore minutes per cubic meter (Fig. 3), where *Q* is the number of spores released as aerosol at the source. The number of spores inhaled is the dosage multiplied by the breathing rate. On the innermost contour of Fig. 2, for example, a person breathing 0.03 m^3 min^{-1}, as for a man engaged in light work (*33*), would inhale 3 × 10^{-9} *Q* spores.

The calculated dosage at Abramovo is more than an order of magnitude lower than that at the ceramics factory. This suggests that sheep, reported to be more susceptible to inhalation anthrax than are monkeys (*34*), are also more susceptible than humans.

It has been suggested that if Compound 19 was the source, there would have been many more cases in its close vicinity than farther downwind (*13*). This expectation may be misleading, for as a cloud moves downwind it also widens. The total crosswind-integrated dosage will therefore decrease more slowly with distance than does the dosage along the centerline. In the present case, whereas the calculated centerline dosage decreases by a factor of 40 between 0.3 and 3 km downwind, the crosswind-integrated dosage decreases by a factor of only 4. Depending on the dose-response relation, the crosswind-integrated attack rate may decrease even more slowly than this. Considering, in addition, the lack of information regarding the exact locations of people in Compounds 19 and 32 at the time of exposure, the distribution of cases is not inconsistent with a source at Compound 19.

More detailed comparison of the geographical distribution of cases with the calculated distribution of dosage would require knowledge of the precise locations of individuals in relation to the plume, the number of spores released as aerosol, and the relation between dosage and response for the particular spore preparation, aerosol, and population at risk.

By far the largest reported study of the dose-response relation for inhalation anthrax in primates used 1236 cynomolgus monkeys exposed to an aerosol of the Vollum 1B strain of *B. anthracis* (*26*, *35*). This provided data that, when fitted to a log-normal distribution of susceptibility to infection, gave a median lethal dose (LD_{50}) of 4100 spores and a slope of 0.7 probits per log dose (*26*, *36*). This LD_{50} may be compared with an LD_{50} of 2500 spores obtained in an experiment done under identical conditions with 200 rhesus monkeys (*35*) and with a U.S. Defense Department estimate that the LD_{50} for humans is between 8000 and 10,000 spores (*8*). For a log-normal distribution with LD_{50} = 8000 and slope = 0.7, the dose causing 2% fatalities, as recorded at the ceramics pipe shop, approximately 2.8 km downwind of the source, is nine spores. According to the Gaussian plume model we have used, this dose would be inhaled by individuals breathing 0.03 m^3 min^{-1} at the pipe shop if the aerosol released at the source contained 4 × 10^9 spores. In contrast, a release 150 times larger is estimated if the calculation is based on an LD_{50} of 4.5 × 10^4 spores, which has been obtained for rhesus monkeys by other investigators (*37*), and if it is assumed that spores act independently in pathogenesis and that all individuals are equally susceptible (*38*). This estimate would be lowered if allowance were made for nonuniform susceptibility. If these divergent estimates bracket the actual value, the weight (*39*) of spores released as aerosol could have been as little as a few milligrams or as much as nearly a gram.

In sum, the narrow zone of human and animal anthrax cases extending downwind from Compound 19 shows that the outbreak resulted from an aerosol that originated there. It remains to be learned what activities were being conducted at the compound and what caused the release of the pathogen.

REFERENCES AND NOTES

1. P. S. Brachman, in *Bacterial Infections of Humans: Epidemiology and Control*, A. S. Evans and P. S. Brachman, Eds. (Plenum, New York, ed. 2, 1991), pp. 75–86.
2. *Health Aspects of Chemical and Biological Weapons* (World Health Organization, Geneva, Switzerland, 1970).
3. *Posev* (*Frankfurt*) **1**, 7 (1980).
4. B. Gwertzman, *New York Times*, 19 March 1980, p. 1.
5. I. S. Bezdenezhnykh and V. N. Nikiforov, *Zh. Mikrobiol. Epidemiol. Immunobiol.* **1980** (no. 5), 111 (1980).
6. *Veterinariya* **1980** (no. 10), 3 (1980).
7. *Chelovek i Zakon* **117** (no. 9), 70 (1980).
8. Defense Intelligence Agency, "Soviet biological warfare threat," DST-1610F-057-86 (U.S. Department of Defense, Washington, DC, 1986); L. H. Gelb, *New York Times Magazine*, 29 November 1981, p. 31; J. P. P. Robinson, *Arms Control* **3**, 41 (1982).
9. R. J. Smith and P. J. Hilts, *Washington Post*, 13 April 1988, p. 1; M. Meselson, *Fed. Am. Sci. Public Interest Rep.* **41**, 1 (September 1988); I. S. Bezdenezhnykh, P. N. Burgasov, V. N. Nikiforov, unpublished manuscript, "An Epidemiological Analysis of an Outbreak of Anthrax in Sverdlovsk" (U.S. Department of State Language Service, translation 126894, September 1988).
10. N. Zhenova, *Literaturnaya Gazeta* (Moscow), 22 August 1990, p. 12; *ibid.*, 2 October 1991, p. 6; S. Parfenov, *Rodina* (Moscow), May 1990, p. 21; Pashkov, *Isvestiya* (Moscow), 11 November 1991, p. 8; V. Chelikov, *Komsomolskaya Pravda* (Moscow), 20 November 1991, p. 4.
11. N. Zhenova, *Literaturnaya Gazeta* (Moscow), 13 November 1991, p. 2.
12. D. Muratov, Yu. Sorokin, V. Fronin, *Komsomolskaya Pravda* (Moscow), 27 May 1992, p. 2.
13. L. Chernenko, *Rossiyskiye Vesti* (Moscow), 22 September 1992, p. 2.
14. A. A. Abramova and L. M. Grinberg, *Arkh. Patol.* **55** (no. 1), 12 (1993).
15. ———, *ibid.*, p. 18.
16. L. M. Grinberg and A. A. Abramova, *ibid.*, p. 23.
17. F. A. Abramova, L. M. Grinberg, O. V. Yampolskaya, D. H. Walker, *Proc. Natl. Acad. Sci. U.S.A.* **90**, 2291 (1993).

18. Russian Federation, statute 2667-1 (4 April 1992).
19. L. Grinberg, personal communication.
20. V. M. Popugaylo, R. P. Sukhanova, M. I. Kukhto, in *Current Problems of Anthrax Prophylaxis in the USSR* (Moscow, 1974), p. 50.
21. S. R. Hanna, G. A. Briggs, R. P. Hosker, *Handbook on Atmospheric Diffusion* (U.S. Department of Energy Report No. DOE/TIC-11223, Washington, DC, 1982).
22. D. E. Davids and A. R. Lejeune, *Secondary Aerosol Hazard in the Field* (Defence Research Establishment Suffield Report No. 321, Ralston, Alberta, Canada, 1981).
23. A. Birenzvige, *Inhalation Hazard from Reaerosolized Biological Agents: A Review* (U.S. Army Chemical Research, Development and Engineering Center Report No. TR-413, Aberdeen, MD, 1992).
24. P. S. Brachman, S. A. Plotkin, F. H. Bumford, M. M. Atchison, *Am. J. Hyg.* **72**, 6 (1960).
25. D. W. Henderson, S. Peacock, F. C. Belton, *J. Hyg.* **54**, 28 (1956); C. A. Gleiser, C. C. Berdjis, H. A. Hartman, W. S. Gochenour, *Br. J. Exp. Pathol.* **44**, 416 (1963).
26. H. N. Glassman, *Bacteriol. Rev.* **30**, 657 (1966).
27. A. V. El'kina, *Zh. Mikrobiol. Epidemiol. Immunobiol.* **1971** (no. 9), 112 (1971).
28. J. V. Jemski and G. B. Phillips, in *Methods of Animal Experimentation*, W. I. Gay, Ed. (Academic Press, New York, 1965), pp. 273–341.
29. A. C. Chamberlain, *Proc. R. Soc. London A* **296**, 45 (1967).
30. T. W. Horst, in *Atmospheric Sulfur Deposition*, D. S. Shriner, C. R. Richmond, S. E. Lindberg, Eds. (Ann Arbor Science, Ann Arbor, MI, 1980), pp. 275–283.
31. Å. Bovallius and P. Ånäs, in *Proceedings of the 1st International Conference on Aerobiology*, International Association for Aerobiology, Munich, West Germany, 13 to 15 August 1978, A. W. Frankland, E. Stix, H. Ziegler, Eds. (Erich Schmidt, Berlin, 1980), pp. 227–231.
32. G. A. Cristy and C. V. Chester, *Emergency Protection Against Aerosols* (Report No. ORNL-5519, Oak Ridge National Laboratory, Oak Ridge, TN, July 1981).
33. D. S. Ditmer and R. M. Grebe, Eds., *Handbook of Respiration* (Saunders, Philadelphia, 1958).
34. G. A. Young, M. R. Zelle, R. E. Lincoln, *J. Infect. Dis.* **79**, 233 (1946).
35. J. V. Jemski, personal communication.
36. C. I. Bliss, *Ann. Appl. Biol.* **22**, 134 (1935).
37. H. A. Druett, D. W. Henderson, L. Packman, S. J. Peacock, *J. Hyg.* **51**, 359 (1953).
38. H. A. Druett, *Nature* **170**, 288 (1952).
39. R. Scherrer and V. E. Shull, *Can. J. Microbiol.* **33**, 304 (1987).
40. We thank A. V. Yablokov, Counsellor to the President of Russia for Ecology and Health, for letters of introduction; Ural State University and its then rector, P. E. Suetin, for inviting us to Ekaterinburg; S. F. Borisov, V. A. Shchepetkin, and A. P. Tiutiunnik for assistance and advice; members of the Ekaterinburg medical community and the Sverdlovskaya *Oblast* Sanitary Epidemiological Service for discussions, notes, and documents; interview respondents for their cooperation; P. N. Burgasov, USSR Deputy Minister of Health at the time of the outbreak, for documents regarding livestock deaths; and People's Deputy L. P. Mishustina for the administrative list of those who died. I. V. Belaeva assisted with interviews. We also thank B. Ring, W. H. Bossert, P. J. M. Cannone, M. T. Collins, S. R. Hanna, J. V. Jemski, D. Joseph, H. F. Judson, M. M. Kaplan, J. Medema, C. R. Replogle, R. Stafford, J. H. Steele, and E. D. Sverdlov. Supported by grants to M.M. from the John D. and Catherine T. MacArthur Foundation and the Carnegie Corporation of New York. This article is dedicated to Alexander Langmuir.

RESEARCH ARTICLE

Analysis and Expression of a Cloned Pre–T Cell Receptor Gene

Claude Saint-Ruf,* Katharina Ungewiss,* Marcus Groettrup, Ludovica Bruno, Hans Joerg Fehling, Harald von Boehmer

The T cell antigen receptor (TCR) β chain regulates early T cell development in the absence of the TCRα chain. The developmentally controlled gene described here encodes the pre-TCRα (pTα) chain, which covalently associates with TCRβ and with the CD3 proteins forms a pre-TCR complex that transduces signals in immature thymocytes. Unlike the λ5 pre–B cell receptor protein, the pTα chain is a type I transmembrane protein whose cytoplasmic tail contains two potential phosphorylation sites and a Src homology 3 (SH3)–domain binding sequence. Pre-TCRα transfection experiments indicated that surface expression of the pre-TCR is controlled by additional developmentally regulated proteins. Identification of the pTα gene represents an essential step in the structure-function analysis of the pre-TCR complex.

T cell development takes place in discrete steps during which the TCR genes are rearranged and expressed in temporal order. During development of TCRαβ-expressing cells the TCRβ gene is rearranged and expressed before the TCRα gene (*1*, *2*). Without TCR rearrangement the development of T cells is arrested at an early stage (*3*–*5*). By introducing TCRβ transgenes into mice that are defective for rearrangement of antigen receptor genes, it was shown that TCRβ proteins, in the absence of TCRα chains, are sufficient to promote early T cell development (*6*–*8*). Although such mice are still rearrangement-defective, their immature thymocytes (which express neither the CD4 nor CD8 proteins) begin to express CD4 and CD8 coreceptors, transcripts of the TCRα locus become detectable (*7*), and the number of thymocytes increases (*6*–*8*). Introduction of TCRβ transgenes into normal mice suppresses rearrangement of endogenous TCRβ genes (*9*, *10*). The TCRβ transgene is expressed on the cell surface in the absence of TCRα proteins in both normal (*11*) as well as in rearrangement-defective mice (*7*, *8*, *12*) in an 80-kD disulfied-linked complex and as a glycosyl-phosphatidylinositol (GPI)–linked 40-kD monomer.

The presence of the TCRβ chain in the 80-kD complex suggested that either the complex was a homodimer or that an unknown TCR chain was involved that may affect T cell maturation. A glycosylated chain of 33 kD (gp33) is paired with TCRβ proteins in a TCRβ-transfected immature T cell line (SCB.29) from severe combined immunodeficient (SCID) mice (*12*), but could not be identified in normal thymocytes (*12*, *13*). The gp33-TCRβ complex of SCB.29 cells is associated with CD3 proteins (*8*, *12*) and cross-linking of TCR chains initiates Ca^{2+} mobilization. This suggested that this TCRβ complex could be responsible for the developmental progression observed in TCRβ transgenic, rearrangement-deficient mice, whereas the TCRβ GPI-linked monomer could represent a transgenic artifact (*14*, *15*). We have now cloned the gene encoding gp33 and examined its structure and expression. Because of its properties, the gp33 protein was named the pre-TCRα (pTα) chain.

Pre–T cell receptor α (pTα) expression in immature T cells. The pTα chain can be identified by two-dimensional (diagonal) gel electrophoresis, in which the disulfide-linked pTα protein under reducing conditions migrates away from the diagonal just underneath the TCRβ protein (*12*) (Figs. 1 and 2). The analytical method was scaled up to obtain sufficient amounts of pTα protein for microsequencing. In a first attempt a 20-amino-acid-long NH_2-terminal sequence was obtained; a peptide of the 18 NH_2-terminal residues was synthesized and injected into rabbits to obtain a pTα-specific antiserum. The antiserum was tested for binding to the pTα protein. To this end lysates from the TCRα-negative SCB.29 cell line as well as the TCRαβ-expressing B6.2.16BW hybridoma (*12*) were precipitated with the monoclonal antibody (mAb) F23.1 to $V_\beta 8$ proteins (*16*). Precipitates

C. Saint-Ruf is at the Unité INSERM 373, Institut Necker, 75730 Paris, Cedex 15, France. K. Ungewiss, M. Groettrup, L. Bruno, H. J. Fehling, and H. von Boehmer are at the Basel Institute for Immunology, CH-4005 Basel, Switzerland.

*The first two authors contributed equally to this work.