

Fiftieth anniversary of trisomy 21: returning to a discovery

Marthe Gautier · Peter S. Harper

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“In reality, discoveries are due to people at the edge of the formalised groups of researchers”

Pierre Laszlo

Fifty years ago, I was the co-author¹ of the first paper that showed the presence of an additional chromosome (Lejeune et al. 1959) in the syndrome identified by Langdon Down in 1866 and commonly known as “mongolism” in France at the time. This, the first autosomal chromosome aberration recognised in the cells of the human species, was named trisomy 21. I thought it would be of historical interest to bring my own personal testimony as an actor in that discovery.

A historical background

Going back to 1958 involves rediscovering the context and the firmly held beliefs of that period. Although it had been accepted for decades that human beings possessed 48 chromosomes, Tjio and Levan (1956) demonstrated in 1956 that

there were in fact only 46. This did not affect many people, apart from a few geneticists, and for a long time 48 was still the figure taught in schools. This stage, which seemed simple, was followed by other more important stages that brought us closer to finding the origins of life; however, this did not create such a stir in the media as the launch of the first artificial satellite Sputnik (meaning “fellow traveller” in Russian) a few months later, which drew us closer to finding the origins of the universe. Science advances on different levels, depending on the disciplines.

It had been necessary to wait 30 years before the genetic laws of peas, as observed by Johan Mendel or ‘Brother Gregor’ of the Augustinian Monastery of Brno, was recognised by biologists. Soon after this, Nettie Stevens revealed the existence of sex chromosomes in a certain species of beetle (Gilgenkrantz 2008). In about 1910, Morgan’s work on *Drosophila*, the providential fruit fly with its amazingly fast reproduction rate and giant chromosomes, laid the first foundations of cytogenetics (Morgan et al. 1925). Had it not been for the attitudes of Alexis Carrel (1912 Nobel Prize winner) during the Occupation (Gilgenkrantz and Rivera 2003), his cell culture experiments would have been widely used. However, a long sequence of errors and failures discouraged the researchers. And it was not until 1949, and then only on cat neuronal cells, that Barr and Bertram (1949) discovered the existence of a body only in the female nucleus; this in fact proved to be a general phenomenon that indicated the presence of two X-chromosomes. The cytological explanation for this (lyonisation) fell to Lyon (1961). Simple swabs of the mucous membrane in the mouth then allowed inter-sexual states to be diagnosed.

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¹ By a slip of the pen that I dare not interpret, my name was wrongly entered as “Marie Gauthier”. The error was corrected in subsequent publications.

54	The discovery of trisomy 21, as I lived through it...	Aicardi and Jacques Couvreur, ³ Fulbright scholarship holders, were also on the voyage and also based in Boston. We were the first IHPs to benefit from a scholarship to study in the United States. After 5 days at sea and a slight storm, we sailed in slowly at crack of dawn. The propellers gently fell silent. The skyscrapers of Manhattan stood out stark against a gloriously blue sky. We were the guests of Uncle Sam. Although not exactly bilingual, we were not "immigrants without papers"; we had a 1-year visa.	100
55	The beginnings		101
56	I arrived in Paris in 1942, in the middle of the war, to stay with my elder sister Paulette, an intern at the Gustave Roussy Institute nearing the end of her medical studies. She introduced me to the mysteries of the student world, and warned me: "If you're a woman, and you're not the boss's daughter, you have to be twice as good to succeed". I started on a PCB (first medical degree): easy enough. In 1944, Paulette was killed by the Germans in a showdown at the time of the Liberation. For my grieving parents I, from that moment on, had to be both her and myself: not at all easy. I aimed at the competitions that opened the doors. After my medical clerkship, I was awarded an IHP, an internship at the Paris Hospitals, a post often sought after but rarely gained by women (no woman actually got one until 1885). In my promotion, out of 80 appointed interns, there were only two girls.		102
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63		"As a pilgrim" I am in Boston	109
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65		I had 24 hours to find a shared apartment and buy a bed, chair and table at the local flea markets. Prof. David Rutstein had put together a perfect programme: with Prof. Alexander Nadas, pioneer in the diagnosis of congenital cardiopathy before surgery and with Prof. Benedict Massell, responsible for acute rheumatic fever (ARF). I was also to visit several centres that specialised in ARF: Cleveland, Chicago, San Francisco, Seattle, New Orleans and Washington. The dose of cortisone to be prescribed, and the duration of treatment, was in fact far from being agreed upon. People were also asking whether this "miracle" drug could prevent the onset of heart conditions. The heads of each centre shared their experience and opinions with me, and I learned a great deal, even from the differences. Travelling alone on Greyhound buses (more than ten nights to save on hotel bills) was a brave step; but buses were miles better than planes for appreciating the landscape.	111
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72	After 4 years of wonderful clinical apprenticeship in paediatrics, one of my tutors, Prof. R. Debré, the father of paediatrics, put me forward for a 1-year scholarship at Harvard, offered by a patron who had just founded the SESERAC. ² The subject was child cardiology with the following aims. (1) Eradicating Bouillaud's Disease (also known as acute rheumatic fever) with penicillin and treating sometimes fatal cases of carditis with cortisone, still scarce in France. I dedicated my thesis to the clinical and anatomopathological study of the lethal forms of this disease caused by attacks of beta-haemolytic streptococcus A, an organism that was still very sensitive to low doses of penicillin, which did not arrive in Europe until a late stage, after the war. (2) Creating a department for the diagnosis and surgical treatment of congenital heart conditions in newborns and infants. These were new and fascinating perspectives: learning in order to provide better care and recovery for children...		118
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83		I was given another "job" that I knew nothing about, working as a technician in the cell culture laboratory with fragments of aorta. This was a plus: I worked part time, as I chose, on Sunday if it suited. Who would not want that? A delightful lady technician taught me everything there was to know about cell culture, and even taught me American slang. Everything was at my fingertips in the freezer. I came to know how to examine cultures under the microscope, photograph them and develop the photographs. I compiled dossiers for biochemists working on comparative studies of cholesterol levels in child and adult fibroblasts. I replaced the laboratory manager who was on maternity leave. I spent hours in the great library on the upper floor. I explored the various techniques of cell culture, and recent cardiology data. But at the time, I was not asked any questions on genetics.	129
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90	After some hesitation, I agreed, not without reluctance, to leave family, friends and love for a year, without being able to see them or even telephone (too expensive then). However, my mind was made up, and in September 1955, I took a tearful train journey from Paris to Le Havre and a cabin on the Cunard line's <i>Mauritania</i> (air travel was much too expensive for mere scholarship holders). By chance, two IHP colleagues from the Robert Debré School, paediatricians Jean		136
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² One of his children had just died from Bouillaud's Disease because of a lack of cortisone in France and he had founded the Society of Study and Care for Children with Acute Rheumatic Fever and Congenital Cardiopathy.

³ Jean Aicardi went on to pursue a brilliant national and international career establishing child neurology, and one syndrome is named after him. Jacques Couvreur, meanwhile, divided his life between hospitals and private clients and was the national reference point for the treatment of congenital toxoplasmosis.

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145 The library was a place for meetings and exchanges. We
 146 French were seen as natives of a country that always
 147 needed help with ending its wars and which at the time was
 148 meddling in Algeria! Ever since then, I have pleaded for
 149 and defended all the immigrants of the world.

150 My visa finally expired and I returned on the *Flanders*. I
 151 honoured my debt to my patron, coming back full of
 152 enthusiasm and plans. I arrived early in the morning at Le
 153 Havre. They were waiting for me on the quay... And in
 154 Paris, it was time to come down to earth.

155 New décor

156 The post of head of clinic with Prof. M. Lelong, promised
 157 before my departure, had been given to a colleague in my
 158 absence. The only posts available were at the Hôpital
 159 Trousseau, with Prof. R. Turpin, with whom I had never
 160 been a trainee, extern or intern. We did not know each
 161 other; I was not a pupil of his house! With my friend Jean
 162 Aicardi, who also returned from Boston, there we were as
 163 “heads” (chef de clinique) in September 1956 (Fig. 1). The
 164 clinic offered a poorly paid part time teaching post, but I
 165 needed it to become an assistant and eventually an estab-
 166 lished paediatrician. The atmosphere was like a hospital
 167 department, with its typically French rigid hierarchy, and
 168 the supervisor was a very distant and laconic figure. What a
 169 contrast to the laid-back atmosphere in the United States!
 170 But you have to “work with” before you can flourish and
 171 advance in life.

172 As experienced paediatricians, we knew that this
 173 supervisor was interested in malformations, and
 174 attempting to draw a distinction between innate and
 175 acquired. In 1937, he had mentioned that mongolism
 176 might be due to a chromosome abnormality similar to
 177 that of the Bar mutation in the fruit fly (Turpin et al.



Fig. 1 Professor Turpin's Department in 1957. *First row: first on left, Marthe Gautier, third, Jacques Lafourcade, fifth, Professor Raymond Turpin. Second row, first on left, Jean Aicardi*

1937). He was not the first or the only one to put for- 178
 ward this hypothesis, but he had gone no further at that 179
 time. He turned to fingerprint patterns, for the want of 180
 anything better, in his research into the hereditary nature 181
 of mongolism. In 1950, in London, Penrose (1950) 182
 leaned more towards a triploidy than a trisomy or 183
 monosomy. He had the chance to obtain a testicular 184
 specimen, from a patient, which he gave to Ursula 185
 Mittwoch. The technique and results were uncertain; she 186
 concluded that the cells had “47 or 48 chromosomes” at 187
 a time when the normal number for a human was esti- 188
 mated at 48. However, at least triploidy was excluded. 189

The turning point 190

Then, at the 1956 start of the University Year, the Chief, 191
 returning from the International Human Genetics Congress 192
 in Copenhagen, informed us that the number of chromo- 193
 somes in the human species was not 48, but “46”. He then 194
 voiced his regret that there was nowhere in Paris to produce 195
 cell cultures to count the number of chromosomes in 196
 Mongolism. I was greatly surprised at that remark and, 197
 armed with my American experience, offered to “do what I 198
 could, if I was given some premises”. I knew that I had to 199
 act quickly, without getting it wrong, and succeed at the 200
 first attempt, because the international teams were already 201
 in competition, or about to be, with the rivalry found in the 202
 field of research just as elsewhere. I entered the Sorbonne 203
 to study for a Cellular Biology Certificate. I realised that I 204
 should not count on the support of the research organisa- 205
 tions, as France had not yet recovered fully from the war, 206
 especially in the restructuring of the INH.⁴ Ultimately, 207
 science and politics only go together well when there is 208
 money, which was not the case here. The role of the uni- 209
 versity was one of clinical teaching; it was not equipped for 210
 cutting-edge research. The elite of the hospitals did not yet 211
 realise that the initiative had to come from them. 212

I finally found premises, in the form of an empty former 213
 laboratory with three magnificent pieces of furniture: a 214
 refrigerator, a centrifuge and an empty cupboard with a 215
 low-definition microscope. Water, gas and electricity, and 216
 only me to organise everything; it was the stuff of dreams! 217
 I was not fortunate enough to be offered any finance, and 218
 therefore, at my own expense, I took out a loan to equip 219
 myself with glass items, distilled-water apparatus, and so 220
 on. None of the products needed for culturing was mar- 221
 keted in France. Determined, however, I did not give up 222
 hope. Each week, I prepared the fresh embryo extract, 223
 obtained from 11-day fertilised eggs obtained from the 224
 Pasteur Institute. For the plasma, I used punctures to take 225

⁴ Although the National Institute of Hygiene was created in 1941, 4FL01
 reforms were not made until 1958. 4FL02

226 blood from a cockerel that I had purchased, raised in a
 227 garden at Trousseau. And the human serum was from me—
 228 an economical and reliable procedure. All this has been
 229 reported (Lejeune et al. 1960). I had no desire to use foetal
 230 lung or bone marrow cells; instead, I used connective tissue
 231 explants in which I examined the very young cells in situ,
 232 transplanting the explant when I felt it was sufficiently
 233 grown. There were never any antibiotics or colchicine, as I
 234 feared a possible adverse effect on the integrity of the
 235 karyotype. And there were no subcultures after trypsin
 236 treatment, to prevent anomalies occurring in vitro through
 237 transformed cells. I believe that to be essential to avoid any
 238 form of artefact, such as erratic or induced chromosome
 239 changes. There was a need for proof of initiative, imagina-
 240 tion and discernment in case of failure.

241 Finally, with adaptations, I used the principle of hypo-
 242 tonic medium that had produced the results for Tjio and
 243 Levan (1956), but using a serum base in order not to break
 244 the cell membrane, and finally allowing the slides to dry
 245 before staining them (Rothfels and Siminovitch 1958).
 246 Never any squash, as some recommended (Hsu and Pomerat
 247 1953). Thus, my best preparations were in prometaphase,
 248 without cell membrane breakage, and so produced an exact
 249 figure and beautiful elongated chromosomes, easy to pair
 250 and unbroken. These results were not accomplished until
 251 after a few failures. I had no bibliography, only my notes
 252 taken in Boston. The controls, given to me by the neigh-
 253 bouring surgical department, came from planned surgical
 254 procedures on normal children; and they had 46 chromo-
 255 somes. I now had two AP (Assistance Publique) technicians
 256 who, under my instruction, proved quite remarkable.⁵
 257 I passed on my skills and experience to them.

258 A new arrival at the laboratory

259 I do not remember any visits from the Chief at the begin-
 260 ning. On the other hand, his assistant Jacques Lafourcade
 261 came to see me, somewhat intrigued and initially sceptical
 262 of the adventure's success, especially given the precarious
 263 conditions in which it was undertaken. No doubt he
 264 reported on how my work was going. However, I soon
 265 began receiving regular visits from J. Lejeune. J.L., whom I
 266 did not know, was a trainee at the CNRS and a student
 267 of the supervisor, as witness their joint publications on
 268 fingerprints and the adverse effects of ionising radiation
 269 (Turpin and Lejeune 1954; Turpin et al. 1955; Turpin and
 270 Lejeune 1955; Turpin et al. 1957). I quickly recognised his
 271 interest in the cell cultures, abandoning his magnifying
 272 glass and his statistics on the frequency of the median
 273 palmar crease.

At last, some tissue from Mongol children was
 obtained.⁶ In terms of mitosis, the cells of the Mongol
 children had an unmistakable difference: all had 47 chro-
 mosomes, while the controls had 46. My gamble, which
 was that I would succeed alone with my laboratory workers
 at my technique and above all discover an anomaly, had
 paid off. It is a French discovery, something that was not
 apparent at the start.

The additional chromosome was small, and the labora-
 tory did not have a photomicroscope that would confirm its
 presence and establish the karyotype. I entrusted the slides
 to J.L., who had the photos taken but did not show them to
 me; they were, he said, with the Chief and therefore under
 lock and key. The chromosome appeared to be number 21,
 but it was not christened as such until the Denver
 Conference in 1960.⁷

I am aware of what was said on the side, but I did
 not have enough experience or authority in this medical
 world, whose mechanisms I did not yet understand, to
 deal with it. I was too young to know the rules of the
 game. Kept apart, I had no idea why they did not
 publish earlier. Only later did I understand that J.L.,
 anxious and inexperienced with cultures, feared an arte-
 fact that might wreck his career, which up until then was
 nothing special, but would have suddenly become glit-
 tering had the results been revealed. I suspected political
 manoeuvring, and I was not wrong. On the other hand, I
 had no personal intention of "exploiting" this additional
 chromosome, my professional life was then working
 towards the clinic.

J.L. was now presenting himself as the discoverer of
 trisomy 21. Reporting for the CNRS at the Ionising Radi-
 ation Congress in Canada, and without planning anything
 with Turpin or indeed with me, he mentioned the discovery
 at a McGill seminar in October 1958 as though he were its
 author. I, however, received this letter dated the month
 following that when he visited laboratories in the United
 States (Fig. 2).

At that time, J.L. was brought up to date with the work
 of Patricia Jacobs, who had just found an additional
 X-chromosome in Klinefelter's syndrome (Jacobs and
 Strong 1959; Harper 2006). On his return, we finally
 published with the Academy of Sciences as a matter of
 urgency, in order to overtake the Anglo-Saxon teams
 (Jacobs et al. 1959) rather clumsily, without me being able

⁶ I was very busy at the time, with part time work at Hôpital Bicêtre
 in the CC (congenital cardiopathy) nursery departments, ARF
 consultations, and the start of my private practice.

⁷ It was an irony of cytogenetic history that after the Denver
 classification of 1960, it was subsequently noted that this chromo-
 some was smaller and therefore corresponded to the 22nd pair, but
 everything remained in that order in order not to confuse the wealth of
 literature already available on the subject.

Porradema
le 5 Nov 58

Ma chère Anne,

Grand merci de votre lettre du 20, à laquelle je réponds avec une inépuisable retard - mais, mais!, je n'avais pas été dans une université loin de huit, dans une ville où il n'y a rien à voir le travail devient un vice, faute d'alcool! Un récent mot du patron m'a signalé que vos dernières préparations ont fait l'admiration de moi, de généticien norvégien - cela prouve que ce travail vaut à priori la qualité.

Fick d'ici vers 15 de jour

Fig. 2 Photocopy of a letter sent by J.L. during his voyage to the United States. His reference to “your preparations...” refers to the slides that I had obtained with the first 47 chromosome mitoses

319 to see the photos or be informed about anything. The text
320 was read to me at mid-day one Saturday for presentation on
321 the Monday. This is exceptional in France, as one could, in
322 fact, publish within 3 days in the CRAS (Academy of
323 Sciences reports) in Paris, while a period of 2 months was
324 needed in the international journals. We were therefore the
325 first to publish this discovery in the international scientific
326 world, after talking about it at the McGill Seminar. Con-
327 trary to standard practice, J.L. signed first and my name
328 only appears second. As usual, Prof. Turpin, the leader
329 responsible for the initial hypothesis, signed last. I was hurt
330 and suspected a degree of manipulation, having a feeling of
331 being the “forgotten discoverer”. J.L. then whipped up a
332 great storm in the media, being interviewed by all the
333 papers. A great French discovery...

334 J.L. was then showered with all kinds of rewards, being
335 promoted from CNRS trainee to master of research and
336 winning a gold medal. Without going through the univer-
337 sity channels, he was subsequently named professor of
338 cytogenetics, a title created by Prof. Turpin for his student.
339 This chair ushered in the age of cytogenetics in France,
340 while the discipline was developed right across the world
341 and the fame of J.L. increased. He was awarded the Ken-
342 nedy Prize without asking for me to be associated with it.
343 Progressively, through his participation in numerous con-
344 gresses, he was hailed as the only discoverer and ended up
345 convincing himself of that, to such an extent that Prof.
346 Turpin’s descendants kicked up a fuss through their law-
347 yers. In addition, they lodged in the Pasteur Institute’s
348 archives their father’s articles certifying his seniority in the
349 chromosome-based hypothesis concerning mongolism, which
350 was finally verified. Now, however, “the father of

trisomy 21”, as he is hailed in the media, was becoming a
351 kind of miracle worker⁸ whose efforts at treating trisomy
352 21 left numerous scientists sceptical for not being based on
353 the credible biochemical mechanisms. Subsequently, and
354 in a very coherent continuity, it became possible to make
355 diagnoses before birth in the late 1960s, and then, in 1975,
356 came the voting of the abortion laws that roused JL, a
357 strong believer, to indignation, polemics and battle cries.
358 The laws sparked serious arguments in society and caused
359 a real split amongst cytogeneticists, some of whom wanted
360 prenatal diagnosis to be practised in France. At that time, as
361 André Boué notes,⁹ the Nobel Committee had considered
362 rewarding the discovery of the origins of mongolism. Is it
363 because of the position he adopted that the Nobel Prize was
364 not awarded to Jérôme Lejeune, the only name that the
365 trumpets of fame had sounded?
366

Epilogue

367

The first human autosomal anomaly or the first gonosomal
368 anomaly, in Paris or in Edinburgh? These discoveries were
369 made at the same time, as is often the case when certain
370 scientific and technological levels are reached. If I had not
371 been the first, others would have got there. Whatever
372 happened, I have no happy memories of that period, as I
373 felt cheated in every respect. However, in the history of
374 “discoveries”, many others have also gone unnoticed, like
375 Johann Friedrich Miescher of Basle or Rosalind Franklin of
376 Great Britain, and that in the field of DNA alone.
377

378 Since then, molecular genetics has quickly caught up
379 and overtaken cytogenetics. We now know the physical
380 map of chromosome 21—it has 225 genes, of which only
381 127 are currently identified—and its sequence, produced in
382 2000.

383 Since then also, the respect for women scientists has
384 undoubtedly progressed, as in 2008, the Nobel Prize was
385 awarded not only to Luc Montagnier, but also to Françoise
386 Barré-Sinoussi, for their work on the discovery of the
387 retrovirus responsible for AIDS (Costagliola 2008). There
388 is hope for the future.

Acknowledgments

389

I would like to thank Joëlle Boué and Simone Gilgen-
390 rantz, who encouraged me to revive these very old
391 memories.
392

⁸ Or at least, one who claims to be a miracle worker. 8FL01

⁹ See interview with André Boué, January 2001. History of INSERM: 9FL01
<http://infodoc.inserm.fr/histoire>. 9FL02

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Commentary 468**Fifty years of human chromosome abnormalities** 469

The fiftieth anniversary of the discovery of the first human 470
chromosome abnormalities marks not only a key point in 471
the development of human cytogenetics and the birth of 472
clinical cytogenetics, but it is also a landmark in medical 473
genetics as a whole, providing laboratory foundations for 474
what had until this time been principally a theoretical area 475
of medicine. The increased demand for genetic counselling 476
and the overall development of medical genetics during the 477
following decades were largely based on these initial dis- 478
coveries and the technical advances that rapidly followed 479
to make them suitable for use in a medical diagnostic 480
context. 481

Fifty years on, we have reached the point where human 482
cytogenetics and human molecular genetics have largely 483
fused, so this year, 2009, is an appropriate point for his- 484
torical perspectives on how these early discoveries were 485
made and how the field developed. Hopefully there will be 486
a number of such articles in both the genetics and the 487
history of medicine and science literature, which will col- 488
lectively allow this important period to be assessed criti- 489
cally in a way that was not possible at the time of the 490
events. 491

The accompanying article by Dr Marthe Gautier in this 492
issue of *Human Genetics* (Gautier 2009), translated directly 493
from that written in French and published earlier this year, 494
makes a valuable and unusual contribution to the history of 495
one of the key discoveries—that of trisomy 21 as the 496
chromosomal basis of Down's syndrome. It is valuable as 497
coming directly from the worker most involved in the 498
actual discovery, and unusual in that it brings into the 499
public domain facts concerning the discovery which, while 500
widely recognised in France (Gilgenkrantz and Rivera 501
2003) are little known internationally, and which will 502
prompt a reassessment of the respective roles and contri- 503
butions of those involved in the work. 504

To place this article in context, it is important to rec- 505
ognise that Down's syndrome had been proposed as a 506
possible human chromosome abnormality as long ago as 507
1932 by both Davenport (1932) and Waardenburg (1932), 508
but establishing or refuting this was prevented by the 509

510 limitations of cytogenetic technology and the uncertainty
511 of the normal human chromosome number until the pub-
512 lication of Tjio and Levan (1956), (Harper 2006b), in 1956.
513 Once these obstacles were overcome, multiple groups
514 across Europe (but not initially in America) began the
515 search for chromosome abnormalities in both Down's
516 syndrome and the possible sex chromosome disorders.

517 By the end of 1958 at least four groups were actively
518 studying Down's syndrome, including those of Marco
519 Fraccaro (then in Uppsala) (Fraccaro 2004), Patricia Jacobs
520 (Edinburgh) (Jacobs 1982), and Paul Polani (London)
521 (Polani 2003) in collaboration with Charles Ford (Harwell).
522 As Gautier makes clear in her paper, the Paris workers
523 were keenly aware of this, and of the greater cytogenetic
524 experience and technical resources of the other groups. In
525 the event, the initial, exceedingly brief, paper on trisomy
526 21 appeared in the *Comptes Rendus* of the French Acad-
527 emy of Sciences for January 1959 (Lejeune et al. 1959),
528 virtually simultaneously with the two other landmark
529 papers, both on sex chromosome abnormalities, by Jacobs
530 and Strong (on XXY Klinefelter syndrome, January 31)
531 (Jacobs and Strong 1959) and by Ford et al. (on XO Turner
532 syndrome) (Ford et al. 1959). Any attempt to assign pri-
533 ority to one or other of these contributions is meaningless,
534 especially when the minimal peer review process of the
535 French Academy of Sciences is taken into account (Harper
536 2006a). But there is no doubt that the Paris workers can
537 claim the credit for discovery of the first autosomal chro-
538 mosome abnormality and it is wise of Gautier to restrict
539 their claim to this.

540 It is of interest to consider briefly the other initial studies
541 on the chromosomal basis of Down's syndrome that
542 appeared in 1959. That of Patricia Jacobs, with her clinical
543 colleague John Strong appeared in *Lancet* in April 1959
544 (Jacobs et al. 1959), while the study of Fraccaro, with Jan
545 Lindsten and Jan Böök, was published in *Acta Paediatrica*
546 in September 1959 (Böök et al. 1959). Polani and Ford did
547 not continue their overall study of Down's syndrome, but
548 rather focused on the group born to younger mothers,
549 leading to their discovery of translocation Down's syn-
550 drome, published the following year (Polani et al. 1960). A
551 wider account of this rapid succession of discoveries is
552 given in the author's book, *First Years of Human Chro-
553 mosomes* (Harper 2006a).

554 It can be seen from Marthe Gautier's article and from a
555 previous review of early human cytogenetics in France by
556 Simone Gilgenkrantz (Gilgenkrantz and Rivera 2003), that
557 the widely perceived role of Jérôme Lejeune as discoverer
558 of trisomy 21 requires revision, preferably also in the light
559 of other evidence and documentation from those in Paris at
560 the time but not directly involved in the discovery, since
561 neither Lejeune nor Raymond Turpin, head of the depart-
562 ment, are still living to give current personal accounts. It is

563 of relevance that Gautier herself has kept silence on the
564 exact circumstances of the discovery for the past 50 years,
565 having subsequently made a distinguished career in pae-
566 diatric cardiology, not in genetics. In addition to the 50th
567 anniversary, a further factor making this subject a topical
568 one has been the recent initiation by the Roman Catholic
569 Church of proceedings for making Lejeune a saint, a pro-
570 cess requiring testimony from those involved.

571 Regardless of the significance of Lejeune's own con-
572 tribution to the discovery of trisomy 21, there can be no
573 doubt as to his key role as the leader of the Paris school of
574 human cytogenetics, which over the following decade
575 made a series of major discoveries of human chromosome
576 abnormalities (Lejeune et al. 1963; Lejeune and Lafour-
577 cade 1968) and developed important new cytogenetic
578 techniques (Dutrillaux and Lejeune 1971), giving France a
579 world leading role in this field. It is perhaps this for which
580 he should be remembered, rather than for his association
581 with the trisomy 21 discovery.

582 What general historical conclusions can be drawn from
583 this work and from the reassessments by Gautier and by
584 Gilgenkrantz and Rivera? First, and perhaps most impor-
585 tant is the need for close collaboration and mutual respect
586 between clinical research workers and basic scientists
587 involved. The mutual roles of Paul Polani and Charles
588 Ford, and of Patricia Jacobs and John Strong provide
589 examples, in the first instance allowing distinction of
590 translocation Down's syndrome by focusing on those born
591 to younger mothers—none of the early series contained
592 such cases; the Edinburgh study increased the rigour of its
593 series by inviting Lionel Penrose, world authority on
594 Down's syndrome, to examine the patients, resulting in
595 exclusion of a number that would otherwise have been
596 misdiagnosed. The Paris group was perhaps unusual in that
597 all three of the workers were paediatrically trained, but it
598 also ensured its diagnostic accuracy through the long-
599 standing experience of Down's syndrome of Raymond
600 Turpin, head of the Paediatric unit at Hôpital Trousseau.

601 A powerful impression from Gautier's article is the lack
602 of appreciation or respect for the work of women in sci-
603 ence, even in relation to their key discoveries. This cer-
604 tainly seems to have been present strongly in the Paris
605 group, and the situation is reminiscent of that experienced
606 by Rosalind Franklin in relation to the discovery of the
607 structure of DNA (Maddox 2002). In contrast, Patricia
608 Jacobs received both encouragement and full credit for her
609 work, and is specific that she never encountered prejudice
610 as a woman in science, in Edinburgh or elsewhere (Jacobs
611 2004). Before concluding that the UK record was better
612 than that of France, however, one should remember that
613 Rosalind Franklin received full encouragement and respect
614 while in Paris, only to encounter such prejudice after her
615 return to Britain.

616 A final lesson to learn is that the initial publications
 617 concerning a major scientific discovery may not always
 618 contain the full truth, especially when this concerns the
 619 relative contributions of those involved. It is salutary to
 620 note that it may take 50 years or more for all the necessary
 621 facts to come into the public domain, by which time not all
 622 the participants are likely to be living. In this respect, the
 623 situation for the discovery of trisomy 21 is perhaps compar-
 624 able with that of the work and individuals concerned
 625 with study of the normal human chromosome number in
 626 Lund, where again 50 years elapsed before the first pre-
 627 parations demonstrating 46 human chromosomes were
 628 published (Harper 2006b).

629 The paper by Marthe Gautier published here in Eng-
 630 lish translation will be read with interest by both those
 631 working in genetics and by historians of science and
 632 medicine. It will form a valuable strand of the definitive
 633 history of this chapter of work, along with accounts from
 634 different perspectives, and we should be grateful to
 635 Dr Gautier that, after 50 years, she has set on record her
 636 own perspective as one intimately involved with, and
 637 responsible for, one of the most important advances in
 638 human genetics.

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