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'Patenting for the Public Interest': Administration of Insulin Patents by the University of Toronto

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Abstract : Whereas the norms of the academic world and medical ethics prohibited academics and doctors from applying for patents on medical inventions, the University of Toronto decided in 1922 to file a patent application on the discovery of insulin, covering both the therapeutic substance and the isolation and purification processes developed by the inventors. The University extended its patent to 25 countries in North America, Europe, Latin America, Australia, India and Japan. An Insulin Committee was set up to "administer the patents in the public interest". Toronto University's intention was to use its industrial property rights in a particular way: to control the standards and quality of a potentially dangerous drug, and to prevent the emergence of a monopoly that might limit the drug's accessibility to patients. The administration of insulin patents "in the public interest" was a highly controversial subject during the inter-war years. On the one hand there were those who advocated regulation of the quality of drugs via patents and, on the other hand, those who opposed the idea of the University of Toronto receiving royalties to finance its medical research.

On 23 January 1922 at the Toronto General Hospital, Leonard Thompson, a young diabetic close to death, received an injection of a bovine pancreas extract. He consequently recovered his strength and a satisfying life, provided he received daily injections and observed a strict lifestyle.[i] The extract in question was produced in an artisanal way by a biochemist, James Bertram Collip, who was assisting two young doctors, Frederik Grant Banting, a surgeon, and Charles Herbert Best, still a student, in the University of Toronto physiology department headed by physiologist John James Richard Macleod. The event caused a sensation in the medical profession and was headline news, both locally and internationally. The enterprise that was then launched was the purification of an unknown substance first called *iletin* and then *insulin*[ii]. Its

production was initially entrusted to the Connaught laboratories situated on the Toronto university campus. Later, due to the complexity of the operation, it was transferred to the US laboratory Eli Lilly[iii]. Insulin is an extraordinarily effective but dangerous drug, and manufacturing it raises the crucial question of the regulation of its production and sale. Faced with this question the discoverers decided to patent their discovery, despite prevailing hostility in the medical profession as regards drug patents. Anticipating the criticism that this type of patent was likely to trigger, they wrote to Sir Robert Falconer, Vice-Chancellor of the University, on 25 May 1922 to present and justify their planned patent and to request the university to manage it. In his positive reply Falconer announced the creation of a committee, soon known as the Insulin Committee (IC)[iv].

The University of Toronto (UT), which was thus the main player on the scene, was not a small institution. It was at the heart of the 'progressive' movement which had striven, from 1880, to 'introduce' science into university education and especially that of medicine. This endeavour was encouraged and assisted by the state which, even more so than in the US, reinvested in the country's universities that it had temporarily neglected[v]. Robert Falconer, vice-chancellor, clergyman and classicist, was a fervent supporter of the British Empire and encouraged the recruitment of several professors and researchers from Britain. One of them, Macleod, a Scott trained in Aberdeen, Leipzig and Cambridge, had already acquired a sound reputation in the scientific community prior to 1922 as chairman of the American Physiological Society. He was a specialist in intermediary metabolism and especially in the normal and pathological metabolism of carbohydrates, on which he had published a book[vi]. This configuration facilitated links with Britain in the Anglo-Canadian system that was to be set up by UT. The Connaught laboratory, baptised the Antitoxin Laboratory, was an original, semi-state organization created in May 1914 along the same lines as the Pasteur Institute[vii]. Housed

in the medical building of the UT Department of Hygiene, its mission was not to make a profit but to combine the promotion of health policies, through the production of low-cost vaccines for free distribution, with the development of research, by creating a source of funding for university laboratories. In the early years financial profit was not the objective of the promoters of the UT laboratories. We thus witness the setting up of an initial form of association between UT and a commercial organization, under the aegis of the state, the guarantor of a function similar to that of a public service and the sale of drugs at cost price or even free distribution. This was the spirit prevailing over UT's policy on the manufacturing and distribution of insulin.[viii]

1- Patents and Medical Ethics: the Dilemma of the University of Toronto

The decision to patent insulin was by no means self-evident for the UT discoverers. Patenting a medical discovery clashed with the university's norms, which proscribed the privatization of the results of academic science[ix], as well as the norms of the medical profession whose code of ethics prohibited its members from appropriating health goods. These were to remain free of any monopoly and of any financial gain[x]: 'Since, however, it is contrary to the traditional principles of the medical profession to restrict the production or supply of any substance that may be used for the alleviation of human suffering and is contrary to its ethical code for any physician to derive financial benefit from the sale of such substance …'[xi]. To reach their decision and build their strategy for administration of a medical patent, the discoverers of insulin studied precedents – Macleod cites the patenting of adrenalin in 1900 by an industrial chemist, Takamine, who granted an exclusive license to Parke Davis[xii] – and directly contacted Kendall at the University of Minnesota who had patented thyroxin a few years prior to

that[xiii]. In a well-argued letter dated 10 April 1922, Kendall described the patent for protecting and exploiting thyroxin, and presented his views concerning patents on biological and medical products. He encouraged his colleagues to patent 'the pancreatic active agent', for he considered that patents were an appropriate way of protecting biological and biochemical preparations, and that new patents on substances of therapeutic interest were likely to enable the norms of the medical profession to evolve: 'if this thing is done enough times, and the matter brought up before the medical profession, all the old time prejudice will surely disappear'[xiv]. He then described in detail the scope of the thyroxin patent which covered both the substance and the method used to separate the product. He highlighted the advantages of dual protection of both the product and the production process, which allowed for strong power of control over industry. Yet, to extend the protection of the patent to a substance which did not yet appear to be perfectly isolated and defined, Kendall suggested defining it in the patent in terms of its physiological and clinical effects: 'in regard to the patent, you will of course be unable to patent the substance as yet, but you should have no trouble with patenting the process, and you can make this very broad, so broad that I feel sure you can safeguard the preparation. The substance can be defined in your case by its physiological action, as nothing similar exists'[xv].

Kendal then informed Macleod of the system for administering the thyroxin patent. This patent was co-owned by the University of Minnesota, the Mayo brothers, and the discoverer himself. The latter two parties had sold their rights to the University on condition that it organized the commercial exploitation of the drug in the interests of the medical profession. To administer its patent and transfer the invention to industry, the University of Minnesota set up an ad hoc committee, on which Kendall was secretary. The committee responsible for managing the patent chose to grant an

exclusive licence on thyroxin to the firm Squibb and Sons. The licence was drafted in such a way that the University of Minnesota retained very strict control over the preparation, sale and price of thyroxin. It used the patent to organize the production of this drug and its market: 'we have limited the manufacture to one firm and we control every world of advertising that firms puts out. We have a right to control their factory and twice a year the books are gone over and a financial adjustment is made. We have set the price at which thyroxin is sold …'. The University of Toronto was strongly inspired by this setup. The 'inventors' of insulin likewise gave their rights to the university, which set up an insulin committee in 1922 to administer its patents and manage relations with industry. Toronto drafted licences which were very similar to the one described by Kendall as regards regulation of industrial production, the sale of the drug and control over its price. As far as royalties were concerned, the University of Minnesota received half of the profits of Squibb and Sons, between 5 and 10% of the price of the drug, while the University of Toronto applied a rate of 5%. The two universities did nevertheless differ on one point: the exclusivity of the licence. While UT decided to grant an exclusive licence to Eli Lilly to develop the technology and production of insulin, it was clearly agreed from the date of the concession of this licence, in May 1922, that that exclusivity was only temporary, for an experimental period of one year, and that it would be replaced in May 1923 by non-exclusive licences with several pharmaceutical firms. While the question of the exclusivity or non-exclusivity of the licence did not seem to be a matter of concern to Kendall, it was a key principle in the policy of the University of Toronto, which wanted to prevent any monopoly on the manufacturing of insulin.

The last point addressed by Kendall concerned inventors' possible remuneration. Although Kendall noted that he had requested no personal remuneration, the agreement

between himself, the Mayo brothers and the university stipulated that the governors of the university were authorized to pay him a share of the university's revenue, not exceeding 10% of the total. This was a sensitive issue since it concerned a well-established rule in medical ethics, in terms of which doctors were to have no interest in the product of their inventions[xvi]. Kendall hoped that the University of Toronto would establish the same system of financial profit-sharing and agreed that this would promote a change of medical research norms in a way that would favour inventors: 'If this thing is done by several people, it may eventually result in the inventor finally sharing in some of the proceeds. I can see no more reason why the man that separates the active constituent of the pancreas should not share financially as much as the man that makes a new wireless telephone'. Here Kendall established a strict equivalence between the inventor of a new medicinal substance and the inventors in other branches of industry. He thus disregarded the status of exception attached to inventions and inventors in the medical domain. This was by no means the point of view of the co-discoverers of insulin.

The University of Toronto was deeply concerned about administering its patents on the basis of the ethical principles of the medical profession. It wanted to use its industrial property not as an exclusive tool of appropriation for drawing a rent or collecting a share of the profits for the inventors, but as a means to regulate the industry and the drug in conformity with the ethical code of doctors, and to defend patients' interests. The inventors justified their patent by a paradox: they were to use it to prevent any inclination to create a monopoly: '…it was decided that the patents should be assigned to the Board of Governors of the University of Toronto to be held by them for the sole purpose of preventing any other person from taking out a similar patent which might restrict the preparation of insulin'[xvii]. In addition to its role of preventing a

commercial monopoly, the patent gave the university an authority to set the standards of the new drug, control the quality of its industrial production, and regulate the conditions of its marketing. In the university's hands the patent was to be a tool to discipline the industrial world, to organize the distribution and use of the new drug, and to guarantee its accessibility.[xviii]

Although the University of Toronto wanted to use its industrial property to promote the public good, the discoverers of insulin remained divided as to the legitimacy of such a patent. Banting did not want his name to appear on any patent. Consequently, the first patent applications filed in the US in May 1922 carried only the names of Best and Collip, and not Banting's. Eventually Banting agreed to co-sign the invention because of a risk of US patents being invalidated if any of the main inventors were not cited[xix]. Lilly's IP adviser suggested a possible arrangement between medical ethics and the patent: 'I fully realize the ethics of the medical profession regarding patents, and sympathise with the position of Dr Banting; but as far as I can ascertain, there is no prejudice, at least in the United States, against a medical man applying for a patent when the patent is transferred to an institution and he does not personally derive any benefit therefrom …'[xx]. Agreement on the devolution of the inventors' rights to the University of Toronto was reached on 15 January 1923, a few days before the second version of the patent application, signed by Banting, Best and Collip, was filed at the US patent office. This agreement was completed by an arrangement concerning the splitting up of income from royalties, for the benefit of a university research fund and non-profit institutions hosting inventors.

2- Which Format for Insulin Patents

Once the decision had been taken to patent insulin, the question of the format of the (process and/or product) patent(s) had to be answered. Would it be best to patent only the process for preparing insulin (and any possible variants), or also the isolated substance, even imperfectly purified – given that the scope of a product patent was far broader than that of a process patent? Whereas ownership of a process patent left the first inventor at the mercy of subsequent inventors who would be able to develop more efficient processes for isolating and purifying the product, the owner of a patent on the substance would be able to control future improvements to processes, which would be dependent on the basic patent. Because academics at Toronto had little experience in patenting biological products of medical interest, the patent format was negotiated and co-defined by the different protagonists, that is, university colleagues – primarily Kendall –, the legal adviser of the UT insulin committee, Riches, the Eli Lilly patent adviser, G. Schley, and the R&D manager at Lilly, G. Clowes.

We have seen that Kendall recommended to Macleod the patenting of both the insulin separation method and the substance itself, even if that substance was not yet perfectly isolated and purified. He suggested getting round this difficulty by defining the substance in terms of its physiological effects, in so far as there was no comparable substance, according to him, that had similar effects for treating diabetes[xxi]. Eli Lilly's scientific director pointed out the scope of the protection offered by a product patent: 'It is extremely important to take out a product patent for if you do not take this precaution someone else will undoubtedly devise a process differing sufficiently from yours to enable them to manufacture the same product without restriction'[xxii]. He believed that this type of protection was possible, even if the product obtained at the time was not perfectly purified. Patents could always be taken out later, on improved substances: 'Then with further progress and the production of purer products, further patents should

be taken out to cover the purer products about which more definite specifications can be given'[xxiii]. Intellectual protection had to try to cover, as well as possible, an invention and a product in the making. It is true that Lilly was directly interested in the soundness of Toronto's intellectual property rights, to which it had the exclusive license from May 1922. The firm participated directly in the delimitation of the university's patents.

The substance covered by the patent application was thus defined by its physiological and therapeutic effects, as Kendall had suggested: 'a potent pancreatic product or extract in sufficiently pure concentrated form for repeated administration to human patients and which had the physiological and therapeutic characteristics of removing the cardinal objective symptoms of diabetes mellitus in patients and reducing the percentage of blood sugar in laboratory animals …'[xxiv]. Thus, clinical characteristics defined the patentable more than did chemical ones[xxv]. The scope of the patent was relatively broad since it encompassed all sufficiently purified pancreatic extracts containing the anti-diabetic active principle: " ... in the case of applications signed by Banting, Best and Collip for patents in Canada, the USA and elsewhere, this was an extremely wide range, perhaps not broad enough to cover a synthetic preparation, but certainly broad enough to cover each and every type of preparation, whether now or ever patented or not, which has been used to date as an "Insulin" '[xxvi]. The novelty of the extract isolated by Toronto University compared to previously available extracts, especially the preparations of the German researcher Zuelzer who had obtained a patent in the US in 1912, was justified by the fact that the new extract could be administered continuously to patients without side-effects: 'the results of these experiments were not considered sufficiently satisfactory to justify the continued use of the extracts in the treatment of men because of the presence in the extracts of toxic substances …'[xxvii]. Once again, it was a clinical fact that was used to attest to the higher level of purity and

novelty of the product patented by Toronto. The patent did give some indications on the steps of the purification process, and on the substances that had to be separated, but the data were fragmented and incomplete, for instance: 'a substance … practically free from inert associated gland tissue and injurious substances … ' (Paragraph 3); 'a substance … practically free from proteins and other injurious substances' (Paragraph 4).

The scope of the patents filed by Toronto was taken into consideration by rivals such as J. Murlin of the University of Rochester, who wanted to collaborate with an industrial laboratory, the Wilson Laboratory, to produce a pancreatic extract. Murlin was fully aware that he had to obtain Toronto's authorization to develop his production with the Wilson laboratories. He therefore challenged the legitimacy of Toronto's patents on the grounds of the non-patentability of natural substances: 'The two preparations[xxviii] and perhaps others yet to be invented should stand squarely on their merits. Of course we all depend on the same substance which has been invented by none of us but by nature itself. It is only the method of preparation which we claim is original'[xxix]. If the product was not patentable, Murlin would easily be able to develop a parallel production to the one controlled by Toronto, with the argument that his preparation method was different.

In the autumn of 1922, Dale and Dudley, representatives of the Medical Research Council (MRC) at the University of Toronto and the Eli Lilly laboratories in Indianapolis[xxx], were highly critical of the Canadians' intellectual property rights. First, they criticized the scope and lack of precision of Toronto's patent claims: 'It appears to us that the patent claim itself is inherently weak. As drafted, it is so wide and vague that it seems very doubtful whether a claim for original invention can be sustained'[xxxi]. The patent claims were too broad and ill-defined, and were easy to by-pass. For evidence, Dale and Dudley pointed to a competing patent application by Murlin, on an extract of

his invention, the copy of a product commercialized by the Fairchilds laboratories, and especially to the patent filed by Toronto University's industrial partner, Eli Lilly, on a new process for separating insulin. Second, they called into question the patentability of Toronto's results which, in their opinion, were more a discovery than an invention: 'the fact is that the real and essential discovery, or invention, is not the process of making the extract, but the fact that a suitably made extract will effectively replace the hormone which is defective in diabetes. This discovery cannot in itself be protected by patent'[xxxii]. Dale and Dudley saw in the discovery of insulin an effort that was of a scientific rather than an industrial nature: 'It must be borne in mind that a degree of novelty and priority in discovery, which is quite sufficient to establish a worker's claim for scientific credit among his colleagues, may be wholly inadequate to sustain a claim to the monopoly of pecuniary profit from that discovery, against the ingenuity of commercial rivals'[xxxiii].

We are going to see that intellectual property at the University of Toronto was not as fragile as Dale and Dudley imagined. First, the legitimacy of Toronto's patent claims was never questioned, neither by the patent offices nor by the judges, whether from the angle of non-patentability of scientific discoveries (Dale and Dudley) or from that of natural substances (Murlin). Second, the university was able to maintain its control over the intellectual property of insulin, owing to the extent of the basic patent that it owned, which was an obligatory point of passage in North America[xxxiv], and to the principle of mutualization of patents that it managed to impose on its partners and licensees from 1923. This system of control lasted until the 1950s.

3- How to maintain Control over the Intellectual Property of Insulin? Setting up a Patent Pool in 1923

Between the autumn of 1922 and May 1923, relations between the University of Toronto and its licensee, Eli Lilly, were marked by conflict over insulin patents. On 30 May 1922 the latter had signed an exclusive licence for the Toronto patent in the US and in countries under US influence, for an experimental period of one year, in order to develop the production of insulin on an industrial scale. A few weeks later Lilly moved from copying to improving the technology: ' …we have already materially simplified the process and considerably lowered the amount of precipitant employed. As soon as our people have succeeded in producing a fairly uniform product by their modified procedure and have determined something regarding its stability they will send on preparations to you to be compared with those Dr Banting and Mr Best are producing … '[xxxv]. In September 1922 Lilly filed an application in the US for its new insulin extraction technology, without advising the Toronto insulin committee, which protested: 'Since this application is very similar to that in the patent filed by Collip and Best and by Best, the Committee is at a loss to understand why it was necessary to file it and instructed the secretary to inform Dr Clowes that the Committee disapproved of the filing of this patent'[xxxvi].

Toronto University's fear was twofold. First, the filing of this patent was likely to interfere with the examination of its own patent applications which were being processed by the US patent office. Their approval might be refused or delayed, which would leave the way open to infringement and could compromise the system of control that Toronto wanted to set up on insulin. Second, the university was concerned that this new patent, also very broad since it covered the extraction process and the product obtained, would eclipse its own patent. The new, more effective separation technology developed by Lilly, and the purer and more stable insulin thus obtained, could make Toronto's patents obsolete.

The risk of the licensee surpassing the licensor's technology and patent had been foreseen in the licence signed between the two parties in May 1922. The agreement provided for adjustments that the licensee might make (Article 10), and any improvements that it was authorized to patent (Article 11) and had to communicate and grant back to the licensor: '…full and complete information regarding such methods shall be communicated by the party of the second part *(Lilly)* to the said party of the first part (*Toronto*) for use in the preparation of the said extract' (Paragraph 10)[xxxvii]; 'if the methods referred to in Paragraph 10 are patentable the said party of the second part agrees to apply for patents at the expense of the party of the first part, in the Dominion of Canada and such country or countries as the party of the first part may designate, except the United States of America, and shall assign to the party of the first part such patents upon being requested so to do' (Paragraph 11)[xxxviii]. The 'grant back' clause on patents of improvement did not concern the US[xxxix]. We see that the licence negotiated in 1922 had a flaw which put UT at its licensee's mercy.

Lilly tried to reassure the University of Toronto: the patent application would simply be a routine procedure of the firm's legal services, of little importance. G. Clowes nevertheless admitted that the filing of this patent did have a technological and industrial value for the Indianapolis firm. Lilly wanted to protect the first results of its research investments in a context in which the university's patents had not yet been approved and the first rivals were already on the scene[xl], and to secure its industrial strategy: ' …this patent is taken out by Eli Lilly and Company to safeguard themselves and protect in some measure the large amount of developmental work which they have carried out at very great cost in the course of the last two or three months'[xli]. Clowes simultaneously reaffirmed Lilly's wish to cooperate. He offered to make available to the University of Toronto all the details of the technology that the firm was busy developing, and even

said that UT could duplicate the production unit that Lilly was busy testing in Indianapolis: 'If you want to install a similar plant, our engineers will be glad to put any information they possess at your disposal'[xlii].

But this proposal failed to remove the obstacle weighing on UT's intellectual property rights in the United States. In March 1923 Defries, director of the Connaught laboratories, drew his colleagues' attention to the reality of this type of threat: 'This latter patent contains claims which are of a broader character than those contained in the Banting, Best and Collip patent'[xliii]. In a memorandum dated 3 April 1923 the insulin committee's IP adviser described a preoccupying situation as regards UT's product and process patent claims[xliv]. If Lilly's patent referred to the work of Banting, Best and Collip, it was simply to demonstrate that its own product was far purer and more stable than that of the UT researchers. Riches showed that Lilly's patent covered both the new process and the product, and that if a product patent was granted, it would give Lilly an absolute monopoly on US production. This type of patent clearly rivalled the product and process patent that the university had applied for in the US: 'In my opinion, these product claims have been drawn for the deliberate purpose of securing to the Eli Lilly Company a monopoly in the United States of the production and sale of Insulin by any method whatsoever and conflicts with the policy of the University in doing the greatest good for the greatest number'. Riches shows that Lilly's product and process claims corresponded precisely to Toronto's patents and even used knowledge that had been communicated to the Lilly research director during interaction with UT researchers. In drawing up the list of overlaps and borrowings, Riches developed an argument for a future patent battle and concluded that the final settlement of the scope of the Walden[xlv] patent was crucial. If the patent was limited to the purification method, it did not encroach on the university of Toronto's intellectual property. However, if it laid claim

to a preparation containing the anti-diabetes hormone, it encompassed not only the Walden method but also that of the UT inventors.

To regain control in the US, the University of Toronto devised several strategies. First, it tried to get its partner to rewrite its patent application in such a way that it limited its scope. It pointed out that the Walden patent was subsidiary to and dependent on the university's patent. The repetition of UT's injunctions and Lilly's proposed amendments up to the spring of 1923 shows that the former was unable to obtain what it wanted. It then decided to counter-attack directly in the US by filing an application for a rival patent by a researcher at the University of Saint-Louis, Shaffer, who had developed a principle similar to the one patented by Lilly. Toronto had thus found in Shaffer an ally to challenge the priority of Lilly's patent: ' …Prof Shaffer considered Eli Lilly and Co. were not warranted in applying for these patents since the idea of precipitation of the isoelectric point was not original with them'[xlvi]. The outcome of this struggle was that Lilly finally agreed to hand over its patent to the University of Toronto, which was then responsible for rewriting, filing and administering it. The Walden patent was one of the insulin patents that the university managed up until the 1940s[xlvii].

For what reasons did Lilly decide to cede its intellectual property rights to the University of Toronto when in fact it was perfectly entitled to file a US patent on an improvement developed by its research laboratories? It is likely that the pharmaceutical firm was reluctant both to lose the benefits of intense scientific cooperation with the university and to bear the costs of conflict with the scientific and moral authority of the discoverers of insulin. This authority was related to the actual discovery of insulin, to the beneficial effects of the new drug on patients, and to the medical ethics defended by the university, for exploitation of the drug. Engaging in a legal battle over the intellectual

property of insulin would run counter to the ethical considerations that the university upheld. It was better to opt for the university's patronage: 'While we consider ourselves legally and morally entitled under our agreement with the committee to take the strongest possible patents on our discoveries and whilst we are not in the least concerned about Shaffer's claims as our process is superior to and differs essentially from his and we are satisfied of our priority nevertheless we would not consider doing anything that might embarrass Toronto University'[xlviii].

Lilly agreed to an important sacrifice: in so far as its patent was administered by the university, and the university intended to grant non-exclusive licences to several pharmaceutical laboratories, it was likely to lose its pre-eminence in insulin extraction technology and in the US market. G. Clowes therefore suggested placing all patents that might be filed by future licensees of Toronto University in a common patent pool, placed under the university's control. Forced to share its intellectual property, Lilly wanted the principle of sharing to apply to all the licensees. The mutualization of IP rights was thus suggested by the firm, concerned as it was not to be excluded from the future insulin market by another licensee: 'It would protect us against any accident depriving us of the industrial leadership to which we are certainly entitled and yet permit open competition as desired by the committee'[xlix]. On 10 April 1923 the insulin committee endorsed this policy: 'It was decided by all licensees that any patents taken out by them shall be assigned to the University of Toronto who may authorize other licensees to use the methods patented, in other words the policy of pooling the patent was decided upon'[l]. A month later the subject of extending the patent pool to British patents was discussed, once again on Lilly's suggestion.

At the same time, the principle of a patent pool corresponded to Toronto University's policy of guaranteeing accessibility of the invention to multiple firms which

could then compete to minimize the cost of the drug. The mutuality of the industrial property was a way of precluding a monopoly and of facilitating the circulation of new technologies and their swift, untrammelled adoption by all the licensed firms, as well as the diffusion of the best production standards. Finally, the university was able to retain control over new inventions and, from there, to practise the 'good governance' that it wanted for insulin, without any risk of being short-circuited by a licensee. The patent pool thus reinforced UT's authority over the entire industry that was in the process of being established. Although Clowes and his legal adviser were at one stage concerned about a possible contradiction between the creation of this patent pool and US anti-trust laws[li], the pool was nevertheless created and was effective, at least until the Second World War. It was the University of Toronto that rewrote and filed the Walden patent, henceforth reduced to a process patent[lii]. In December 1923 the insulin committee considered that Lilly was not justified in receiving royalties for the use of the Walden patent by other firms in the US. Lilly's patent had clearly fallen into the common pool. The University of Toronto then decided to extend the Walden patent to foreign countries, to strengthen its intellectual property on the basis of a more effective process than the one initially patented under the names of Banting, Best and Collip. It subsequently received the British Duddley patent and later, in the 1930s, patents filed by the Danes[liii]. All these inventions were placed at the disposal of various licensed laboratories. One question nevertheless remained in suspense: did industrial know-how have to be pooled and communicated along with the patents? Clowes was obviously not in favour of the disclosure of the technical details that he had communicated in writing to the University of Toronto, concerning the implementation of the Walden process – apart from the contents of the patent[liv]. Yet the training programme that Best designed

for future licensees stipulated that visitors could obtain 'the intricate details of the method', at the discretion of the Connaught laboratory staff[lv].

4- Regulating the industrial production and market of insulin by means of patent licences

The distribution of operating licences on its patents was an opportunity for the University of Toronto to define a particularly broad regulation of the drug, including the sharing of innovations via the patent pool, the control of sound manufacturing practices by licensed firms, the testing of their products, and the monitoring of their advertising and prices.

The university endeavoured first to organize a non-monopolistic market for insulin by distributing non-exclusive patent licenses – even if, paradoxically, it started by granting an exclusive license to Eli Lilly for an experimental period of one year. This exclusive relationship was justified by the concern to establish more efficient scientific cooperation with a single partner in order to co-develop industrial manufacturing processes faster, to standardize the product and to relieve patients[lvi]. The choice of Lilly was justified by the firm's scientific and industrial experience in the field of biological products[lvii]. The exclusive licence was conceived of here as an ideal means for technological learning between two partners, and not as the means to establish a monopoly. Hence, when G. Clowes asked for an extension until January 1924 to enable Lilly to recover its investments and to 'saturate' the US market, his request was refused[lviii]. The university reaffirmed its policy of non-exclusive licences. First, it had previously announced its intention to grant licences to other firms once the industrial process had been improved enough, and this stage had been attained. Second, the MRC

in the UK distributed non-exclusive licences to several industrial laboratories from the outset. Third, the committee thought that the distribution of licences to several firms would favour the availability and accessibility of the product, and especially low prices. Fourth, the committee highlighted the fact that this type of extension would expose the university to criticism for favouring one firm above others. Despite the loss of its exclusive licence in May 1923, Lilly was to retain a strong competitive advantage over its rivals, owing to this early cooperation with Toronto University and to the anteriority of its scientific and industrial investments. The advantage acquired in terms of knowledge and know-how proved to be lasting.

The procedure of granting licences included an evaluation of the candidate laboratories' scientific and technological capacities: 'no licence should be granted by the party of the first part – Toronto – to any person, firm, corporation or association until the party of the first part shall have approved of the scientific staff of such person, firm, corporation or association' (Article 21)[lix]. In so doing, the licensor, the University of Toronto, issued a quasi certification of good manufacturing practices to the firms to which it granted a licence[lx]. Special attention was paid to quality control procedures: ' …none of the licenced products shall be used or sold by any licensee before an inspection of the plant has been made and the party of the first part is satisfied that a proper control of the preparation and testing of the licence product are possible in such plant'[lxi]. In order to evaluate the capacities and competencies of its future licensees, the university sent them a questionnaire[lxii]. The licence applicant had to describe his production site and his experience in the production of biological products. He had to indicate whether he had previously been engaged in the production and commercialization of pancreatic extracts used in the treatment of diabetes and, if so, had to undertake to cease that production in order to obtain authorization to produce UT's

insulin. The questionnaire also concerned the composition, experience, training and publications of the scientific staff that would be in charge of production. Would the firm's chemists be trained in biochemistry? Who were the bacteriologists who would be in charge of quality control? Finally, the licence applicant had to indicate from which sources he intended to obtain his raw material – in this case, pancreases. In the questionnaire filled in by the Airlington Chemical Company laboratories in New York[lxiii], the respondent noted that 'in the past, we have had no difficulty in obtaining fresh glands – adrenal, thyroid, pituitary, ovarian, etc. in any quantity required from any one of several New York abattoirs … '. The Airlington Chemical Company attached a three-page documented letter to complete the information relative to their biological product manufacturing units, to the control of the sterility of these products, and to the content of the laboratory's scientific publications. They relied on Toronto University for training and even the selection of the staff that would be in charge of insulin production[lxiv]. This prior control of the licensee's scientific and industrial capacities was not simply a formality. The insulin committee refused several applications when it considered that the laboratories were not sufficiently equipped and experienced.

The insulin committee also refused to grant a licence to any laboratory that was already engaged in the production of pancreatic extracts for the treatment of diabetes, other than UT's insulin, to avoid any confusion that might compromise the reputation of insulin as a treatment for diabetes. In 1923 it refused twice to grant a licence to The Digestive Ferments Company of Detroit, which produced a pancreatic extract for several firms.

Licences established the University of Toronto's right to control the quality of batches produced by licensees. These tests were to be carried out in a special laboratory created for that purpose by the insulin committee. In September 1923, when new

licences were distributed, the committee decided to re-equip the laboratory and to set it up on the premises vacated by the Connaught laboratories. There it was engaged in the routine work of controlling licensees' samples and in defining insulin standards. The knowledge that it accumulated was coveted, as attested when Squibb and Sons tried to recruit the head of the laboratory, Mr Orr, in 1924, and the committee decided to raise his salary, since he could not easily be replaced.

The licences granted by the University of Toronto established the principle of control over the prices practised by licensees and provided in detail for that control procedure. Regulation of insulin prices was one of the main objectives of the University which wanted to maintain the new drug's accessibility, in the interests of patients. In case of disagreement over prices, the licence provided for the appointment of an arbitration committee composed of three auditors, one paid by UT, a second by the licensee, and the third by the two parties. This committee's opinion would be final. The licensee would have the option either to readjust his price in line with the arbitration committee's evaluation, or else to terminate the agreement[lxv]. Owing to the industrial expertise of the Connaught laboratories, the University of Toronto was in a position to know exactly what the production costs of insulin were, and thus to regulate its licensees' selling prices[lxvi]. Lastly, the licence established a control over the licensee's advertising: 'The party of the second part – the licensee – shall not issue any literature regarding any substances covered by this contract until it has been approved by the party of the first part – Toronto'. Control over advertisements for drugs was generally a particularly important aspect of regulation policies[lxvii].

By distributing its licences in the early 1920s, the University of Toronto extended its regulatory powers into a field that was to become the domain of future drug laws and agencies: the evaluation of good practice in industrial manufacturing; the creation of a

test laboratory devoted to quality control of products prior to their commercialization; and control over advertising. In 1941 the Insulin Amendment Act required that each batch of insulin produced in the US be tested and certified by the Pharmacology Division of the FDA. Yet this law contained a special clause concerning tests run by the UT insulin committee, 'pursuant to a licensing agreement entered into prior to the date of enactment of Public Law 366, 77th Congress, 1st session, 1941'. US regulations ratified the precursory role of Toronto's licences as regards drug control and recognized the insulin committee's control laboratory. In 1942 Eli Lilly took the initiative of sending its samples for control to the FDA laboratory only. The firm pointed out that since UT's basic patents had fallen into the public domain, it no longer considered itself obliged to have its products approved by the university's insulin committee[lxviii]. The Commissioner of Food and Drugs replied, very diplomatically, that the FDA laboratory was indeed able to carry out these tests, but that it would not refuse the results of tests carried out by the UT insulin committee[lxix].

5- Relations between the University of Toronto and the MRC concerning the Management of Insulin Patents

From May 1922, as it filed its patent applications in Canada and the US, the University of Toronto approached the MRC to offer it its insulin patents for the UK and Ireland[lxx]. The aim was to extend its control over the production and sale of the new drug in the British Isles, on the basis of principles similar to those applied by the University of Toronto in North America, that is, disinterest in personal gain for the inventors, and prevention of commercial appropriation of the drug[lxxi]. The MRC was a strong ally for extending the university's insulin regulation policy. At one stage UT even

considered entrusting it with the management of insulin patents for the whole of Europe. The MRC declined, however, as it preferred to avoid putting the British state in a difficult diplomatic position in case of patent disputes with a friendly country[lxxii].

Initially sceptical, like much of the medical world, the MRC sent Henry Dale to Toronto with his colleague Dudley, a biochemist. It wanted to control insulin production in the UK and hoped furthermore to play a key part in defining a policy to govern drug manufacturing. To this end it participated in drafting the Therapeutic Substance bill, passed in 1927[lxxiii], and wished to exploit the introduction of the new remedy to strengthen that role.[lxxiv] Within the MRC Henry Dale, future Nobel Prize winner (in 1936) for his work on chemical transmitters of nervous conduction, specialist in the standardization of drugs, and formerly with the Wellcome Laboratories, was at home in the international scientific community. He was to conduct the international insulin standardization process with brio.

Although the MRC had doubts as to the soundness of UT's insulin patents[lxxv], it accepted the university's offer, on three conditions. The first was that it would be given the necessary know-how for the reproduction of the insulin extraction technology in the MRC laboratories, since this know-how was not described in the patent application filed by the University of Toronto in Britain[lxxvi]. The MRC was aware that its power of control depended, among other things, on the possession of that secret know-how: 'Nobody in England can make or test Insulin satisfactorily without information which the patent does not give, but which we can supply'[lxxvii]. The second condition was that it would not be obliged to defend the patent received in case of disputes over infringement. It considered that such disputes were inevitable in view of the supposed fragility of the UT patent and the commercial value of the insulin market. Yet the MRC was not particularly concerned about the fragility of the UT patent. It was the moral authority of the Council that would

make the patent sound and act as a dissuasion of infringement, not the intrinsic soundness of the patent: '…we think it is very doubtful whether such a challenge would be made, if the Council's position and their reasons for accepting the patent were made clear in the first instance'[lxxviii]. The third condition was that it had total freedom to use this patent. Without a predetermined industrial plan, the MRC wanted to be free to exploit the patent itself or to grant operating licences to firms, as well as exclusive or non-exclusive licences. Finally, the MRC agreed to receive these patents in so far as they enabled it to offset the absence of regulation of drugs of biological origin – 'It is, apparently, generally admitted that control from this Government Department of Biological Standards would be the ideal method, if it could be applied' (Dudley's report) – and to develop its own policy in this domain.

The MRC conceived of several strategies for producing the new drug[lxxix]. The first consisted in entrusting the production of insulin to one or more industrial laboratories and exercising control over their activity via patent licences. In this configuration the National Institute for Medical Research (NIMR) would carry out the control tests on each batch of insulin, before delegating all or part of these tests to industrial firms. This industrial model was similar to the one set up by the University of Toronto for the United States. The second production strategy consisted in entrusting insulin production to the NIMR or to another non-commercial laboratory, at least for an experimental period, before transferring it to industrial laboratories. This model was similar to the one that existed in Canada where insulin was produced by the Connaught laboratories in the institutional framework of the University of Toronto. The MRC experts nevertheless thought that this system of production would be able to supply only a very limited number of clinicians and that it was expensive. The third strategy consisted in spreading insulin production out across the hospital laboratories in which the tests took place, and

which worked in close collaboration with researchers at the NIMR. This type of hospital-based production had been practised experimentally in the US, primarily by Dr Woodyatt in Chicago. Dale and Dudley recommended that the MRC adopt hospital production on a small scale, at least during the clinical trial period[lxxx], while starting to negotiate with those industrial laboratories that agreed to the Council's supervision.

The MRC's licence policy had to combine contradictory conditions. First, the small size of British abattoirs compared to North American ones limited the number of licensees, to avoid them rivalling one another and to organize a rational exploitation of pancreatic resources. Second, the MRC did not want to establish a monopoly on this industry. Finally, production sites had to be located close to abattoirs to ensure a fresh supply of pancreases. Due to these constraints, one or two licensees were chosen in the London area and a single firm or group of firms was selected around large cities like Liverpool or Edinburgh. In the spring of 1923 the MRC had granted six licences in the UK. It foresaw strict control over the insulin produced: each batch had to be tested by the NIMR and could not be commercialized before being certified by the Council. The licence also regulated prices, advertising and presentation of the drug, very much like that of the University of Toronto.

Despite its reservations on the legitimacy and viability of insulin patents, the MRC did recognize the utility of such patents for controlling the drug industry and market: 'I am inclined to think that the original policy, of controlling production by patent … has already served its real purpose'[lxxxi]. In fact the MRC filed a patent on a British process, the rights for which it granted to UT for Canada and the US. Yet a major difference came between the two, concerning the university's collection of royalties. The conflict broke out in 1924 during the proposal to transfer the rights of the English Duddley patent to UT. The MRC agreed to put its patent rights into Toronto's patent pool, provided that

the university did not receive royalties on the English invention: 'Council will assign Dudley's patent rights in Canada and the United States to Toronto University but is obliged to make the condition that no royalties shall be charged'[lxxxii]. A proposition of this nature put UT into a tight spot: how could the university justify the fact that it received no royalties on the Dudley patent but that it received 5% of the sales on the Banting, Best and Collip patent? What were the MRC's arguments against royalties? First, the MRC was a public, medical, non-profit organization: 'In pursuit of theses objects, however, the Council has not thought it consistent with their duty, whether as a government department or as a body of workers in medical science, to charge any kind of royalty … '. Second, the collection of royalties would necessarily weigh on patients and medical institutions, whereas the UT's main objective in filing these patents had been to relieve them both. Third, the only valid justification for patenting medical inventions was the control that patents allowed over the drug industry and trade. Obtaining financial gain from these patents, even for medical research purposes, was proscribed. The University of Toronto nevertheless defended its royalties on the basis of the cost of the tests it performed free of charge for North America, whereas British firms had to pay for the service provided by the NIMR. The university also pointed out the fact that the English patent, on a new process, depended on its basic patent and that its royalty policy was therefore justified, at least for North America. During this controversy the MRC showed its wish to 'teach the University of Toronto a lesson' on the right use to which medical patents should be put. Note that this debate is recurrent in the history of drug patents[lxxxiii]. Should medical research be financed by the rents levied on drug patents – in which case there is the risk of being accused of burdening patients with the price of drugs?[lxxxiv] Or should medical research rather be financed by the state?

Conclusion

The policy of 'administering medical patents for the public good, developed and applied by the University of Toronto in the early 1920s, was an impressive novelty at a time when the manufacturing and sale of drugs were subject to little control. When insulin was put onto the North American market in 1922 there was no specific and effective apparatus to regulate drugs, neither in North America nor anywhere else in the world. Control over the manufacturing and sale of drugs was simply part of a more general system of monitoring food, alcohol and hallucinogenic substances. In the late nineteenth century, among an impressive number of drugs that were hardly effective or even harmful, there was a proliferation of active remedies such as digitaline, morphine, vitamins, certain hormones, antipyretics and the first 'chemotherapeutic' molecules such as Ehrlich's salvarsan. However, most of these drugs were not standardized. Within the same firm products varied from one batch to the next and differences between firms were the rule. In the UK and two of its former colonies, the US and Canada, a law was passed in the latter half of the nineteenth century to punish – at least in principle – the 'adulteration' of drugs[lxxxv]. This Act also broadened the functions of the Agriculture Department's Division of Chemistry, which became the Bureau of Chemistry, the future FDA (Food and Drug Administration).

In no country do we find an effective apparatus for controlling the *efficacy* of drugs sold; only conformity with the information supplied by the laboratory was verified[lxxxvi]. The American Medical Association (AMA), that created in 1905 the Council on Pharmacy and Chemistry as an advisory body on pharmaceuticals and chemicals, did nevertheless publish information on the efficacy of new drugs in the

section of its journal, the JAMA, devoted to new drugs not listed in the pharmacopoeia. This was an indispensable tool for controlling drugs, and insulin was included at a very early stage.[lxxxvii]

In the US the 'ethical' pharmaceutical industry counted on the development of a so-called scientific medicine to justify drugs which complied with the standards of the US Pharmacopeia or the National Formulary. Leading pharmaceutical firms started to see the advantage of state control over the drug market, which favoured the elimination of the small unreliable companies swamping the market with their so-called 'patented' drugs that in reality had obtained no patent. Eli Lilly was one of these new firms which made scientificity and product standardization its slogan. In Canada, regulation of the sale of drugs was first managed by the provinces and inspired by the measures taken in the UK and the US. In 1908 the Proprietary Medicine Act required a clear description on the label of the exact composition of any drug not registered in the official pharmacopoeia. But most states lacked the means for systematic verification of the conformity of drugs sold. Moreover, no proof of the efficacy of a drug was required prior to its commercialization. Drugs were bought freely by consumers, with the exception of opiates and narcotics.

In this context the novelty of the University of Toronto's policy was threefold:

1. In the fields of intellectual property, academic research and the regulation of drugs, the university's policy was driven by the discoverers of insulin's mistrust of industry and their fear of possible abuses in the 'commercial exploitation' of drugs. These abuses could concern the establishment of a monopoly likely to impose restrictions on the supply of a drug considered essential for many patients, or the hasty distribution of insufficiently controlled preparations. The insulin patenting policy helped to shift the commonly accepted norms in the medical profession and academic

world: rather than refusing IP rights altogether, it could be useful to own a patent for the sake of medical ethics and to protect patients[lxxxviii]. The idea here was not to use the power of the patent to create a commercial monopoly or to extract a rent, but to make it the instrument of a drug biopolicy inspired by the public good. To that end, intellectual property had to be free of commercial goals, monopolies on production and sale, profit-sharing for inventors, and perhaps the collection of royalties. On the latter point the MRC wanted the UT policy to go even further and to eliminate any objective of financial gain, even if it was justified by medical research. In the hands of an academic organization like Toronto, or a public agency like MRC, patents became a means to discipline industry and trade.

The University of Toronto managed to impose a policy of mutualization of intellectual property rights on inventions concerning insulin. It employed a sound legal argument: the priority of its basic patent that it intended to use to counter any new process claim. The university also benefited from the moral authority associated with its researchers' discovery and with the humanitarian goals that it had set for administering its patents. Although the principle of pooling patents had been suggested by its first licensee, Eli Lilly, who hoped thus to maintain its position in the market ahead of other licensees, UT pooled inventions primarily to prevent a monopoly. As long as it was accessible to new licensees, so as not to violate anti-trust laws, the patent pool was a means for preserving the openness of the drug market, an incentive for price control, and a way of facilitating the rapid circulation of available inventions. This solution, which had been experimented by the US government during WWI in the aeronautics field for national defence purposes[lxxxix], was new in the pharmaceutical field. It is by no means insignificant that the mutualization of intellectual property took

place in two areas of exception as regards intellectual property: national defence and public health[xc].

2. The power of patents also authorized UT and the MRC to introduce the regulation of production and commercialization of insulin that no institution in Canada, the US or the UK was authorized to apply at that time. This power of control enabled the MRC to compensate for the absence of adequate legal regulations to control therapeutic products in the UK. Such regulations would have rendered drug patents futile: 'I hope that we shall have our Therapeutic Substances Bill passed, which could enable us to control the manufacture and testing of a preparation like this by direct licence, without reference to patents of any kind'[xci]. In fact the insulin affair afforded an opportunity for the MRC to assert its existence in the field of drug regulation and to contribute to the drafting of this bill. Patents on insulin were also valuable for applying the standards defined by the scientific and medical community, and even for educating doctors and patients in the use of high-quality insulin. [xcii] The control exercised via patents was eventually extended to use of the drug by the medical profession and patients. Use of medical patents for the purpose of controlling the quality of health products was the main subject of debate in March 1939 at a conference of the American Medical Association on medical patents. The question was 'patents for profit' or 'patents for quality control'?[xciii] Two cases were presented and discussed: that of serums for the treatment of scarlet fever, and that of insulin patents. In both cases the patents held by universities were used to set up measures for controlling product quality, with which licensee laboratories had to comply. The patent holder selected industrial laboratories with the scientific and industrial capacities judged adequate to meet quality standards. In the case of scarlet fever, the patent holder did not hesitate to sue firms which refused the quality control linked to the granting of a licence. Intellectual property thus became

a means to standardize medical products: '…Highly potent and accurately standardized scarlet fever toxin and antitoxin are produced only in those countries where the products are protected by a patent'. Henri Dale reached the same conclusion regarding insulin. He cited the example of Denmark where the patenting of insulin was impossible and where only one trade mark was recorded. Control over production was impossible and a firm driven more by financial gain than by the preparation of high-quality insulin hindered the efforts of the local insulin committee.

3- The insulin patent also tells us about the format of drug patents. Paradoxically, whereas medical patents were decried because of the monopoly that they established on the supply of health goods, UT's basic patent on insulin was so broad that it covered a multitude of preparations and put all other inventors in a position of dependence. This paradox was pointed out by the chairman of Parke Davis during the conference on 'medical patents' organized by the AMA in 1939, although he acknowledged the non-monopolistic use that had been made of the insulin patent. We have seen that the power of control of this patent stemmed not only from the scope of its legal protection. It was supported by the moral authority of the University of Toronto and the MRC which tended to dissuade potential infringers. It was also reinforced by the know-how of the laboratories responsible for tests – the insulin committee's laboratory – and production – the Connaught Laboratories of the University of Toronto, and by the laboratories of the National Institute for Medical Research in the UK. All these laboratories developed the insulin technology continuously and filed patent applications throughout the 1920s and 1930s. The power of control of patents was moreover supported by the pool system which placed all patents in the university's fold. To conclude, note one of the originalities of this patent: in the absence of a perfectly pure substance and a chemical definition of insulin, which was to become available only much later, the patented

product was defined by a sufficient degree of purity that was superior to preceding preparations, and by its physiological and therapeutic effects of benefit to the treatment of diabetes.

Notes

[i] Diabetes mellitus is a serious disease that kills within months if untreated. It is characterized by severe weight loss, extreme fatigue, thirst, abundant urine and, from a biochemical point of view, glycosuria (presence of sugar in the person's urine) and hyperglycaemia (high level of glycaemia in the blood).

ii. The name Insulin had already been proposed by Edward Schaffer in 1916 and J. de Meyer in 1909. Iletin was the brand name used by Eli Lilly.

[iii] Bliss, The Discovery of Insulin; Sinding, 'Making the unit of insulin: standards, clinical work and industry', 231-270 .

[iv] This committee consisted of three members of the Board of Governors of the University, including Falconer himself, and sat with an Advisory Committee composed of the four 'discoverers' (Charles Best, Frederik Banting, John J.R. Macleod and Bertram Collip) and the director of the Connaught laboratories. Soon known as the Insulin Committee (IC), it created a small laboratory for carrying out bioassays on insulin produced by the pharmaceutical firms. The committee soon grew and, in addition to academics and researchers, included members from industry and an attorney specialized in patent law, Charles Riches.

[v] Gidney and Millar, 'The Reorientation of Medical Education in Late Nineteenth-Century Ontario: The Proprietary Medical Schools and the Founding of the Faculty of Medicine at the University of Toronto', 52-78.

[vi] Bliss, 1982 ; Michael J. Williams, J.J.R. Macleod: The Codiscoverer of Insulin, 1-125.

[vii] Malissard, Quand les universitaires se font entrepreneurs : les Laboratoires Connaught de l'Université de Toronto et de l'Institut d'Hygiène de l'Université de Montréal, 1914-1972 ».

[viii] Although they were soon incapable of mass producing insulin on their own, the Connaught laboratories retained a strategic role throughout the operation. They were a means of putting pressure on the Eli Lilly laboratories, and a means to control the quality of insulin produced by the US laboratory – even if, as we shall see, the IC set up its own control laboratory.

[ix] Weiner, 'Patenting and Academic Research: Historical Case Studies', 50-62.

[x] Swann, Academic Scientists and the Pharmaceutical Industry: Cooperative Research in twentieth-century America ; Cassier 2004, 'Brevet et santé',185-190 ; Rasmussen, 2004, 'The moral economy of the drug company medical scientist collaboration in interwar America', 161-185.

[xi] Professor Macleod, Statement read by J.J.R. Macleod at the Insulin Committee meeting regarding patents and royalties, 28 April 1924.

[xii] Simon, 'Adrenalin, Epinephrin or Suprarenin? Identifying the true hypertensive principle',1-11. .

[xiii] Rasmussen, 'Developing the Hormones of the Adrenal Cortex', 1-42.

[xiv] Letter from Kendall to Dr J.J.R. Macleod, University of Toronto, 10 April 1922. Kendall noted that the insulin patent would be the third patent on a substance of this type, the second being thyroxin.

[xv] Letter to Macleod, 10 April 1922.

[xvi] Swann, Academic Scientists and the Pharmaceutical Industry ; Cassier, 'Genome Patents Nowadays and Pharmaceutical Patents in the 19th Century: a parallel',1-22.

[xvii] Statement read by J.J.R. Macleod at the Insulin Committee meeting regarding patents and royalties, 28 April 1924, op. cit.

[xviii] In February 1923 a press article considered the patenting of insulin as a way of stimulating the evolution of medical ethics: 'any sufferer who receives the Insulin treatment will have complete assurance that he is obtaining the real thing and he will be not overcharged. The profits would go to medical research: 'the arrangement is thus ideal. It represents "medical ethics" in a really modern aspect', 'A step forward in medical ethics', World’s Work.

[xix] The absence of Banting's signature was particularly problematical as regards the claims concerning insulin as a substance, for Banting was presented as the initiator of the research that had led to isolation of the substance.

[xx] Letter to Mr Clowes regarding US patent for insulin, 22 August, 1922.

[xxi] 'The substance can be defined in your case by its physiological action, as nothing similar exists', Kendall, 10 April 1922.

[xxii] Letter to Mac Leod, 11 May 1922.

[xxiii] Letter to Macleod, 11 May 1922, op. cit.

[xxiv] Patent 1,469,994, United States Patent Office, patented on 9 October 1923.

[xxv] The patent applications contain a scientific article setting out the clinical data of insulin trials. Application of Collip and Best, filed on 22 May 1922, serial n° 562.835.

[xxvi] Memorandum: Agreements with Drs Best and Collip, 14 June 1948.

[xxvii] The authors of the Toronto patent referred above all to the patent filed by the German researcher Zuelzer: 'Pancreas preparation suitable for the treatment of diabetes', G. Zuelzer, Chemische Fabrik auf Actien, Schering, patented on 28 May 1912. Patent 1.027 790.

[xxviii] That of Toronto and his own.

[xxix] Letter to C. Riches, Rochester, 7 October 1922. This argument was not used subsequent to that, although it served in 1943 to cancel the US patent on vitamin D and methods for irradiating foods, 'Patenting University Research', R.D. Apple, ISIS, 1989, 80.

[xxx] See below, Paragraph 5 on relations between the MRC and the University of Toronto for administering patents on insulin.

[xxxi] Report to the Medical Research Council on our visit to Canada and the United States chiefly to examine the 'Insulin' treatment of diabetes, by H.H. Dale and H.W. Dudley, 30 October 1922.

[xxxii] Report to the MRC, Dale and Dudley, op. cit.

[xxxiii] Report to the MRC, Dale and Dudley, op. cit.

[xxxiv] In March 1923 the Eli Lilly scientific director tried to reassure Macleod who was worried about possible attacks on the Toronto patent: 'I do not think that you should pay too much attention to the report you received regarding concerted action on the part of manufacturers to defeat the Toronto patent. This is in all probability purely bluff, as the Toronto patent is a strong basic patent and the two or three manufacturers in the US who are in a position to produce Insulin with satisfactory controls, have too much at stake themselves to care to provoke a fight of this nature' (Letter to Macleod, 14 March 1923). The soundness of Toronto's position stemmed from the scope of its product patent and the small number of rivals who had the know-how to produce high-quality insulin.

[xxxv] Letter to Dr Macleod, 20 June 1922.

[xxxvi] Minutes of the Meeting of the special advisory committee on diabetes, Insulin Committee, 22 September 1922.

[xxxvii] Indenture between the Governors of the University of Toronto and the Eli Lilly Company, 30 May 1922.

[xxxviii] Indenture between the Governors of the University of Toronto and the Eli Lilly Company, op. cit.

[xxxix] In other letters to the University of Toronto, Lilly mentions 'British rights' (telegram of 8 April 1923) that the firm has to pay to UT. Apparently 'US rights' are not included in this obligation.

[xl] In several letters, Clowes referred to the production of the Fairchilds laboratories.

[xli] Letter to Dr J.J.R. Macleod, 27 September 1922.

[xlii] Letter to Macleod, 17 September 1922. Note that despite the developments of the separation method, by the end of the autumn Lilly was faced with problems in producing insulin on a large scale (letter to Macleod, November 1922, in which Clowes talks of a new 'deterioration' in an insulin batch).

[xliii] Letter to President Falconer, 14 March 1923.

[xliv] Letter to Macleod regarding the Walden patent, 3 April 1923.

[xlv] Walden was the inventor of the new process patented by Lilly.

[xlvi] Minutes of the Meeting of the Special Advisory Committee on Insulin, 10 April 1923.

[xlvii] The Walden patent fell into the public domain in September 1946.

[xlviii] Telegram to Professor Macleod regarding the Walden patent, 8 April 1923.

[xlix] Telegram to Professor Macleod regarding the Walden patent, 8 April 1923.

[l] Minutes of the meeting of the special advisory committee on insulin, 10 April 1923.

[li] Telegram to Dr Macleod, 20 May 1923.

[lii] To mark its new authority on this patent, the insulin committee even offered to refund Lilly the expenses incurred in having the initial patent rewritten.

[liii] At the end of the 1930s the insulin committee administered a significant number of industrial property rights. A complete list in 1937 comprised eight different patents for the US and Canada, while the University of Toronto basic patent and the Walden patent retrieved from Lilly were valid in 23 countries. University of Toronto, 14 October 1937.

[liv] Minutes of the meeting of the special advisory committee on insulin, 8 November 1923.

[lv] Minutes of the meeting of the special advisory committee on insulin, 28 November 1923.

[lvi] '… and whereas for humanitarian purposes the manufacture of the said product can be more adequately effected by collaboration with one efficient and reliable commercial firm than by collaboration with several firms', Indenture between the Governors of the University of Toronto and the Eli Lilly Company, 30 May 1922.

[lvii] Cf. Preamble to the patent licence, May 1922.

[lviii] Letter to Dr J.J. R. Macleod, 14 March 1923.

[lix] Agreement between the Governors of the University of Toronto and Eli Lilly, 30 June 1923.

[lx] Today this is the drug agencies' function.

[lxi] Agreement between the Governors of the University of Toronto and Eli Lilly, 30 June 1923, op. cit.

[lxii] We acquired a questionnaire filled out by the Airlington Chemical Company of New York. The insulin committee's archives also indicate that a questionnaire was sent to the Armour laboratories in Chicago on 18 July 1923.

[lxiii] This complete questionnaire consists of seven pages.

[lxiv] Letter from the Airlington Chemical Company, 27 July 1923.

[lxv] Article 20 which stipulates the terms of price control is two pages long.

[lxvi] Memorandum on the course pursued by the University of Toronto in the Development of the Manfacture of Insulin, January 1924.

[lxvii] See Young, The Toadstool Millionaires: A Social History of Patent Medicines in America before Federal Regulation.

[lxviii] Letter to WG Campell, Commissioner of Food and Drugs, Washington, 24 December 1942.

[lxix] Letter to Mr Eli Lilly, W.G Campbell, Commissioner of Foods and Drugs, 6 January 1943.

[lxx] This donation resulted in a complete transfer of ownership to the MRC's benefit. In other countries the University of Toronto retained its rights, the administration of which it delegated to local scientific institutions. Cf. the Lorne Hutchinson Report, 1925.

[lxxi] Letter by Macleod, May 1922.

[lxxii] Letter to Macleod regarding the distribution of insulin in Europe, 19 February 1923, L10216.

lxxiii Abraham, Science, Politics and the Pharmaceutical Industry. Controversy and Bias in Drug Regulation, 48-49. Note that in 1911 the Liberals had passed the National Health Insurance Act in Britain. This law enabled people with an income below a certain threshold, determined by the state, to benefit from a national health insurance fund financed jointly by employees, their employers, and the state. The government thus became a purchaser of drugs who was interested above all in the quality of these products.

[lxxiv] Liebenau, 'The MRC and the Pharmaceutical Industry: the Model of Insulin'

[lxxv] Dudley’s report, October 1922.

[lxxvi] 'So far as I a able to judge from the copy of the filed specification in the British Patent application n° 16360 of June 13, 1922, not all the essential parts of the process of manufacturing insulin are disclosed', letter to Dr Fitzgerald regarding patent rights for Great Britain, 4 July 1922, L10214.

[lxxvii] Duddley’s report, October 1922.

[lxxviii] Dudley’s report, 30 October 1922.

[lxxix] Dudley’s report, 30 October 1922.

[lxxx] Such hospital production was set up to meet local clinical needs. It was even the subject of controversy in 1924 when The Times reported that hospital production costs were inferior to industrial costs. Letter to Macleod, London, 17 March 1924.

[lxxxi] Letter to Macleod, London, 17 March 1924, author: H Dale.

[lxxxii] MRC, 15 March 1924. Letter from Sir W. Fletcher to the Insulin Committee.

[lxxxiii] See, for example, the revival of this debate regarding Aids drugs, Cassier, Correa, "Patent, Innovation and Public Health : Brazilian Public-Sector Laboratories'Experience in Copying AIDS Drugs", 89-107.

[lxxxiv] In a memorandum on patents and royalties, dated 28 April 1924, Macleod was fully aware of this difficulty: 'At present the royalty charged is 5 per cent which means, at current retail prices of Insulin, that in a severe case of diabetes requiring 30 units daily, the yearly tax payable by the patient to the Board of Governors is considerable'. He suggested modulating the rate of royalties in relation to the need to defend patents. He nevertheless failed to mention the financing of university research.

lxxxv. 'Adulteration' means the alteration of the purity or concentration of a drug, compared to its characterization in the official pharmacopoeia. Laws were passed in Britain and subsequently in the US and Canada in this respect. In the UK the Adulteration Act of 1860 led to the Sale of Food and Drugs Act of 1875, while in the US the Pure Food Act (1906) was intended to control the sale of food, drugs and drugs, although it focused primarily on food. Temin, 1980: 18-37.

lxxxvi. Temin, Taking your Medicine. Drug Regulation in the United States, 32 and 33.

lxxxvii. This section is called 'New and Non Official Drugs'.

[lxxxviii] In 1937 an article published in Science, 'Should Medical Invention be Patented?', a jurist, A. Conolly, tried to justify patenting by the medical profession in terms of protection of patients. The debate was also conducted by the American Medical Association which organized a conference on this subject in March 1939.

[lxxxix] 'Institutions for Intellectual Property Transactions: the case of patent pools', R.P. Merges, University of California at Berkeley School of Law, 1998.

[xc] Cassier M , 'Brevet et santé' : 185-190.

[xci] Letter to Macleod, 17 March 1924, Sir H. Dale.

[xcii] Agreement with the Toronto Insulin Committee, 1 January 1924; Sinding, 2002.

[xciii] 'Conference on medical patents' , Journal of the American Association of Medicine, 327-335 ; 'Manufacturers' point of view on medical patents in relation to public welfare' Journal of the American Association of Medicine, 419-427.

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