1962
Jan 8-11, 23-26, 29-31, Feb. 1, 2 and 5.
1964
Oct. 23

BETWEEN:

HOECHST PHARMACEUTICALS OF CANADA LIMITED and FARBWERKE HOECHST AKTIENGESELLSCHAFT VORMALS MEISTER LUCIUS & BRUNING ..... PLAINTIFFS;

AND

GILBERT & COMPANY, GILBERT SURGICAL SUPPLY CO. LIMITED, JULES R. GILBERT LIMITED and JULES R. GILBERT ..... DEFENDANTS.

Patents—Infringement—Validity—Process claim—Utility—Specification of patent—Inventiveness of application of known methods to known materials—Must be both new and useful to support invention—Product claim depending on process claim—Validity of process claim dependent on all or substantially all of products of class produced thereby possessing previously unknown usefulness—Utility of products of process claim consisting of application of known method to known material—Application of known method to limitless class of known materials to produce limitless class of expected products some of which may possess utility—Inventiveness where unexpected utility of certain tested members of the class of products produced forms foundation for sound prediction that all or substantially all members of class possess the utility—Invalidity of patent claim for process for making whole class of substances when no such broad invention has been made despite utility of some of products of class—Distinction between utility of products of invention and utility of specific substances of the class—Burden of proving that processes claimed would not produce whole class of useful substances where class composed of limitless number of substances—Pleading objections to patent—Patent Act, R.S.C. 1952, c. 203, s 41(1).

The plaintiffs are respectively the exclusive licensee and the owner of ten patents, the first of which issued on a parent and the remainder on divisional applications for patents in respect of an invention entitled "Manufacture of New Sulphonyl Ureas". They allege infringement on the part of the defendants of claim 10 in the first nine patents and claim 13 in the last one, the alleged acts of infringement being the sale and use by the defendants of the substance known generically as "tolbutamide", which is the compound claimed by the said claims.

The defendants admit the alleged use and sale of the compound "tolbutamide" but they deny infringement and they also plead that claim 1 in each patent is invalid because *inter alia* not all products produced by the process have utility as claimed, and claim 10 in the case of each patent (13 in the last patent) is invalid because *inter alia* claim 1 was necessary to support it.

Held: That the specifications of the patents in issue should be regarded as purporting to disclose several different inventions, one or more pertaining to a class or classes of substances, another to the single substance known as tolbutamide and several others to the particular

substances claimed in claims 11 to 19 inclusive (14 to 21 in the last patent). This is so because the disclosure does not purport to be one of an invention of tolbutamide alone or of it and a process or processes for its preparation but on the contrary purports to relate to a class of sulphonyl ureas of which tolbutamide is one member, and it proceeds to outline in general terms methods by which ureas of the class may be produced and to assert utility for the substances of the class.

2. That there is nothing inventive in applying known methods to known materials or kinds of materials even if no one has previously applied the methods to the particular materials and even if the result is a new product. To have a patentable invention the products in such a case besides being new must be useful in the patent sense and only if they are both new and useful can they and the process for producing them be the subject of a patent.

3. That in the case of each patent the claim sued on is a claim for the substance known as tolbutamide when made by the process of claim 1 or an obvious chemical equivalent. In each case this is a claim to which s 41(1) of the *Patent Act* applies and assuming validity in other respects such a claim can be valid only if it is accompanied by a valid process claim and is limited to the substance when produced by that process or by an obvious chemical equivalent. Accordingly, in the case of each patent the validity of the claim sued on depends on the validity of claim 1.

4. That claim 1 in each of the patents cannot be supported as a valid claim unless all, or substantially all, members of the class of sulphonyl ureas defined in them possess some previously unknown usefulness.

5. That even if claim 1 in each of the patents were read as embracing only those members of the class which as a matter of practical chemistry or of commercial manufacture could be made, it would still be necessary to the validity of the claim for all, or substantially all, of such members to possess some previously unknown usefulness. If this utility is not common to all, or substantially all, of the members of the class, the process claimed in claim 1, consisting as it does of the application of a known method to known materials or to materials having known chemical features, does not represent an invention of a process at all, let alone a patentable invention of a process.

6. That a patent claim in respect of an invention, the embodiments of which are stated to include a process for the making of a whole class of substances, when no such broad invention has been made, will purport to confer an exclusive property in something which the inventor has not invented, and since the *Patent Act* authorizes the grant of a patent only for an invention which the inventor has made, such a claim will be invalid. Nor can the utility of some of the products of the class save the claim.

7. That in considering the evidence with respect to the question of the utility of the sulphonyl ureas of the class defined in claim 1 of the patents, it is important to distinguish between the utility of "the products of the invention", that is to say, insofar as claim 1 is concerned, the whole group of sulphonyl ureas included in the definition of the claim, and the utility of the specific substances of the class, including tolbutamide, which are cited as examples in the specifications or are described in the evidence.

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8. That it is highly improbable that all, or substantially all, of the members of the infinitely large class defined in claim 1 of the ten patents have either the blood sugar lowering activity to a useful extent or the freedom from toxicity or harmful side effects necessary to render them useful and that there was accordingly no invention as claimed in claim 1 of each of the patents and claim 1 is therefore invalid.
9. That because claim 1 of each of the patents is invalid claim 10 of the first nine patents and claim 13 of the last patent are invalid as well.
10. That while the objections to the patent are pleaded in a confusing manner, the objection which has been sustained is raised, and is thus open to the defendants, by the plea that claims 1 and 10 of the first nine patents and claims 1 and 13 of the last patent are invalid because there was no invention having regard to the common knowledge of the art.
11. That the action is dismissed.

ACTION for infringement of a patent.

The action was tried by the Honourable Mr. Justice Thurlow at Ottawa.

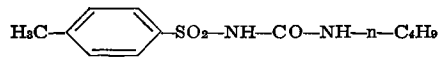
Christopher Robinson, Q.C. and *R. S. Smart* for plaintiffs.

I. Goldsmith for defendants.

The facts and questions of law raised are stated in the reasons for judgment.

THURLOW J. now (October 23, 1964) delivered the following judgment:

In this action the plaintiffs claim an injunction and other relief in respect of alleged infringement of ten patents numbered 582,621 to 582,627 inclusive, 588,513, 588,514 and 590,201, of which the first issued on a parent and the remainder on divisional applications for patents in respect of what is referred to in their specifications as "an invention entitled 'Manufacture of New Sulphonyl Ureas' ". Each of the patents contains a claim (numbered 10 in the first 9 of the patents and numbered 13 in the last) which reads:

> The compound of the formula
>
> 
>
>
> whenever obtained according to claim 1 or the obvious chemical equivalent thereof

and in the case of each of the patents it is this claim alone which the plaintiff alleges has been infringed. There are various technical names which chemists would recognize as referring to the compound of the formula set out in these

claims, one of which is N-(4 methyl benzene sulphonyl)-N1-(n-butyl) urea. This is the name used in the specifications but the simplest name for the substance is the generic name, "tolbutamide".

The second named plaintiff is the owner of the ten patents and the other plaintiff is its exclusive licencee under them. The defendant, Gilbert and Company is a registered proprietorship of which the defendant, Gilbert Surgical Supply Co. Limited is the sole proprietor and it is alleged by the plaintiffs that this defendant has in the ordinary course of business sold throughout Canada tolbutamide in infringement of the patents and threatens to continue to do so and that the other corporate defendant has in the ordinary course of business used, in its plant in Toronto, tolbutamide in infringement of the patents and threatens to continue to do so. These defendants respectively admit selling and using tolbutamide which is admittedly imported from Italy but they deny that they sell or use it or threaten to do so in infringement of the patents. They also plead that claims 1 and 10 of the first nine patents and claims 1 and 13 of the last patent are invalid for a number of reasons some of which will be referred to later in these reasons and one of which is that there was no invention having regard to the common knowledge of the art. The allegations against the remaining defendant, Jules R. Gilbert, need not be considered as the action against him has been discontinued.

The value and importance of tolbutamide lies in its usefulness in the treatment of diabetes. Until shortly before its introduction in the latter part of 1956 treatment of the common form of this illness, known as diabetes mellitis, consisted mainly, if not entirely, in putting the patient on a diet designed to bring about and maintain a proper level of sugar in his blood and if this was not successful or efficient to accomplish the desired result, to administer insulin. Insulin could not be taken orally and thus had the disadvantages associated with administration by needle including those due to the reluctance of the patient and those due to his own shortcomings when administering it himself resulting in administering at times too much and at other times too little. Insulin also had

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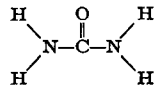
undesirable effects on the tissue adjoining the site of injections carried out over a long period. Early in 1956 a substance known as carbutamide which was known to have blood sugar lowering activity, and which had bacteriostatic activity as well, came into use as an oral antidiabetic, the bacteriostatic activity was undesirable as it tended to destroy bacteria necessary to normal body functions and in October 1956 carbutamide was withdrawn from use in Canada and the United States apparently because of reported undesirable long term effects on the livers and kidneys of patients by whom it had been used. Tolbutamide had already been synthesized and, to some extent, tested before carbutamide was introduced and shortly before the latter was withdrawn it came into use in Canada for the same purpose. The evidence of Dr. J. B. R. McKendry satisfies me that tolbutamide has proven to be a satisfactory oral antidiabetic and has been of considerable value in the treatment of many cases where dieting alone has been insufficient to establish and maintain a proper blood sugar level. Since its introduction at least two other oral antidiabetics have come into use for the same purpose one of which, chlorpropamide, has more pronounced and longer lasting blood sugar lowering activity than tolbutamide but at the same time involves increased danger of undesirable long term effects. These substances are not suitable for the treatment of all types of diabetes nor are they effective for all patients or for what I shall call the severe cases of diabetes mellitis. For these insulin remains the standard remedy. But in a considerable proportion of the cases of diabetes mellitis tolbutamide is effective as a blood sugar lowering agent, and has the advantage of oral administration, and at the same time a satisfactory record of comparatively low toxicity and freedom from harmful side effects.

Before commenting on the specification I shall endeavour to explain some of the chemical concepts and terms which occur in them pertaining to sulphonyl ureas, an understanding of which appears to be necessary to interpret the specifications and to render what follows intelligible.

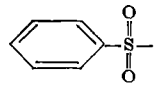
Urea is a single substance having a symmetrical molecular structure containing one atom of carbon, one of oxygen, two of nitrogen and four of hydrogen. The carbon atom has four valencies by which it may be linked to other

atoms in the molecule of a substance. The oxygen atom has two valencies, the nitrogen atom has three and the hydrogen atom has one. In the urea molecule the carbon atom is at the centre with the oxygen linked to it and occupying two of its valencies the other two being linked to nitrogen atoms. The remaining positions of the nitrogen atoms are occupied by the hydrogen atoms. The structural formula may be represented thus:

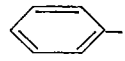


This represents the single substance known as urea but there is a huge group of conceivable substances in which the position of one or more of the hydrogen atoms in the urea molecular structure is occupied by some other atom or group of atoms and these substances are also known as ureas, their chemical names being determined by the names of the substituted atoms or groups and the position which they occupy. Thus such a substance having a sulphonyl group

in the position of one of the hydrogen atoms in urea is known as a sulphonyl urea and since the R in this sulphonyl group may represent any organic radical, the substances which can be regarded as sulphonyl ureas alone constitute an enormous class. One of the commonest of the organic groups is the benzene ring which consists of six carbon and six hydrogen atoms and which on releasing one of its hydrogen atoms may be linked as the R in a group such as RSO_2 which may then be represented thus



When linked in such a group the benzene ring is also known as phenyl and the representation



in this structure is taken as meaning that there is a carbon atom at each corner of the hexagon with a hydrogen atom linked to it in the case of each carbon atom except

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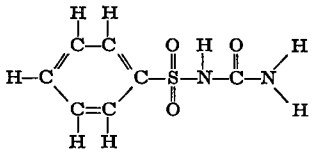
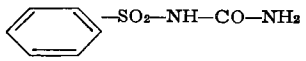
the one which is linked to the sulphur atom. The substance of the formula



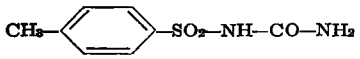
which may more simply be written as



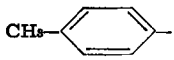
would thus be known as benzene sulphonyl urea.

The benzene ring as well may have substituents in the place of hydrogen atoms in its structure and for identification purposes the corners, starting from that linked to another group, are referred to as ortho, meta and para, para being that at the opposite corner from that linked to another group. At other times the corner may be numbered thus

Accordingly if one has a methyl (CH_3) group in the para or 4 position of the benzene ring of benzene sulphonyl urea the molecule might be represented thus



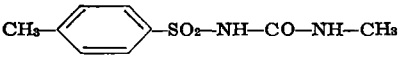
and the substance would be known as para methyl benzene sulphonyl urea or 4-methyl benzene sulphonyl urea. The group para methyl benzene



is a common one in organic chemistry and goes as well by the shorter name, paratoluene, and thus it would be equally correct to name the above mentioned substance paratoluene sulphonylurea. It will be observed that this para toluene sulphonyl group makes up the left hand portion of the molecular formula of the compound represented in the claims sued on.

Most of what I have said so far with respect to substitutions in the urea molecule has been concerned with substitution at one end only of the molecule. When there are substitutions at both ends it is necessary in the naming of

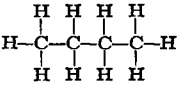
the substance to distinguish accordingly. This is done by referring to the nitrogen atoms as N and N_1 and a substance with substitutions on both nitrogens such as



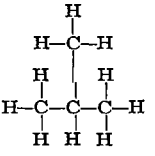
could thus be called N-para toluene sulphonyl-N_1-methyl urea.

As previously mentioned the carbon atom has four valencies and when these are occupied by hydrogen atoms the substance is methane which may be represented as CH_4 or structurally as

The removal of one hydrogen atom from this group leaves CH_3, the group known as methyl, which may be linked by the remaining carbon valence to atoms or groups to form a great variety of compounds. Similarly when two, three or four or more carbon atoms are linked in singly bonded straight chain formation with the remaining valencies occupied by hydrogen atoms, the substances are known respectively as ethane, propane, butane, etc., the name depending on the number of carbon atoms in the chain. In the case of butane, C_4H_{10}, besides the straight chain formation



which is known as normal butane, the carbon atoms may be linked thus



and this substance is known as isobutane. Two different mono substituted derivatives of normal butane are conceivable, the difference depending on whether the linkage to other atoms is made with an end or an intermediate carbon atom and two further different mono substituted butyl groups may be derived from isobutane, the difference again depending on whether the linkage is to an end carbon atom

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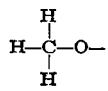
or to the central carbon atoms. The name used to designate a butyl group of the kind wherein the carbon atoms are in straight chain formation and the bonding to other atoms or groups is by an end of the chain carbon atom is normal butyl and this is indicated in formulae by the letter -n- preceding the expression used to designate butyl in the formula. The other butyl groups are respectively known as secondary butyl, isobutyl and tertiary butyl. On referring back to the molecular formula represented in the claims sued on it will be seen that it is an n-butyl group which occupies one of the valencies of the nitrogen atom on the right hand side of the urea molecule.

Groups made up of carbon and hydrogen atoms, whether the carbon atoms are linked in straight chain or other patterns (other than ring patterns), are known by the general name of alkyl groups and this expression is broad enough to include any group of that nature whether it has one or any larger number of carbon atoms. Where such a group instead of being linked directly to other distinguishing components of a molecule is linked through an oxygen atom,



the group consisting of the alkyl group and the oxygen atom is known as an alkoxy group. This term is thus as broad in the number of conceivable groups which it includes as is "alkyl". Further terms to which reference will be made are "halogen" which is the family name of the four elements, fluorine, chlorine, bromine and iodine, and "aliphatic" which, as I understand it, is a term used with respect to all hydrocarbon groups both saturated and unsaturated except the class known as aromatic. Cyclo-aliphatic has a similar meaning but refers to aliphatic, as opposed to aromatic groups in which the carbon atoms are joined in a ring formation.

I turn now to the specifications. The disclosure portion of these is the same in the case of all ten patents the only differences between them being in the claims and in certain supplementary examples which are admittedly not relevant to the present case. The disclosure does not purport to be one of an invention of tolbutamide alone or of it and a process or processes for its preparation but on the contrary

purports to relate to a class of sulphonyl ureas of which tolbutamide is one member, and it proceeds to outline in general terms methods by which ureas of the class may be produced and to assert utility for the substances of the class. Tolbutamide is mentioned from time to time as an example of the class but not until one reaches claim 10 (13 in the case of the last patent) is there any indication that the invention is concerned with anything but a whole class of substances and general methods of producing them. In this respect the specifications resemble that considered in *C. H. Boehringer Sohn v. Bell Craig Ltd.*[1] and for the reasons there given at pages 209 to 215 I am of the opinion that these specifications should be regarded as purporting to disclose several different inventions, one or more pertaining to a class or classes of substances, another to the single substance known as tolbutamide and several others to the particular substances claimed in claims 11 to 19 inclusive (14 to 21 in the last).

The specification of patent number 582,621—omitting immaterial details—is typical of the ten and commences as follows:

> BE IT KNOWN that (several persons whose addresses are set out) having made an invention entitled
>
> "Manufacture of new sulphonyl-ureas"
>
> the following disclosure contains a correct and full description of the invention and of the best mode known to the inventor(s) of taking advantage of the same.
>
> It is known from literature that certain compounds belonging to the class of aminobenzene sulphonamides are capable of lowering the blood sugar value in test animals, for example, of dogs. Thus, for example, para-aminobenzene-sulphonamido-isopropyl-thiodiazole produces a moderate lowering of the blood sugar value in dogs for 4 to 6 hours (compare: Jean la Barre and Jean Reuse, Arch. neerland. physiol. 28 [1947] page 475).

I pause to mention that the substance referred to is also known as IPTD and it was much too toxic for use in the treatment of human beings.

> There are also known certain benzenesulphonyl ureas, such as N-benzenesulphonyl-urea, N-benzenesulphonyl-N'-phenyl-urea, N-benzenesulphonyl-N':N'-diethyl-urea, N-para-toluene sulphonyl-urea and N-para-toluenesulphonyl-N'-phenyl-urea (compare: Chem. Rev., volume 50, pages 28/29). However, these substances have not yet attained any commercial importance. Other products belonging to the series of sulphonyl-ureas are known from U.S. Specification No. 2,390,253 and French Specification No. 993,465.

[1] [1962] Ex. C.R. 201.

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No evidence of the U.S. Specification was given but the French Specification is in evidence and describes a method of preparing an enormous group of ureas embracing as a mere part the whole of the group referred to in the ten patents here in question. The method described in the French patent is also described in the ten specifications here in question and is the method involved in claim 1 of patent number 582,621. The specification continues:

> The present invention provides sulphonyl-ureas of the general formula
>
> $$R—SO_2—NH—CO—NH—R_1$$
>
> in which R represents a phenyl radical which may contain one or two substituents selected from alkyl and alkoxy residues, of which the alkyl group is preferably of low molecular weight, and halogen atoms, or represents an aliphatic or cycloaliphatic hydrocarbon radical containing at least three carbon atoms, and R_1 represents an aliphatic or cycloaliphatic hydrocarbon radical containing at least 2 carbon atoms.
>
> As alkyl residues, of which one or two may be present as substituents in the phenyl radical, and bound, if desired, through an oxygen atom, there may be mentioned, more especially, those of low molecular weight. Especially advantageous are those containing 1 to 3 carbon atoms, but residues containing 6 or more carbon atoms may be present. *When these residues are of higher molecular weight the activity of the products is generally considerably lower.* Instead of being alkylated or alkoxylated, the benzenesulphonyl compounds may contain as substituents in the phenyl residue one or two halogen atoms, preferably chlorine or bromine atoms, or a halogen atom and an alkyl or alkoxy group. The processes for making the sulphonyl-ureas described above are also suitable for making the halogenated benzene sulphonyl compounds.
>
> The primary amines used as starting materials in the above processes advantageously contain saturated or unsaturated aliphatic or cyclo-aliphatic hydrocarbon radicals containing 3 to 6 carbon atoms. However, they may contain radicals of higher molecular weight, but *radicals containing more than 12 carbon atoms generally reduce the activity of the products.*

(The italics are my own.)

With respect to the second italicized statement exhibit H indicates that at 12 carbon atoms the activity has reached zero. This passage however refers only to the substituents on the right hand side of the urea molecule and it may be noted at this point that claim 1 is restricted in that respect to groups containing from 2 to 8 carbon atoms. There follow several pages of general description of the methods-- all of which were already well known to chemists—and of various starting materials of which it is stated that many of them "suitable for use in the present process have been described in literature". Up to the end of this portion of the disclosure there is accordingly nothing whatever to indicate a patentable invention for there is nothing inventive in applying

known methods to known materials or kinds of materials even if no one has previously applied the methods to the particular materials and even if the result is a new product. To have a patentable invention the products in such a case besides being new must be useful in the patent sense and only if they are both new and useful can they and the process for producing them be the subject of a patent. *Vide* Jenkins, J. in *Re May & Baker et al.*[1] at page 281.

The next nine pages of the specification, however, deal with the utility of the products. The specification states:

As has been demonstrated by experiments on animals and in clinical tests, the products of the invention produce a substantial lowering of the blood sugar level. They may be used as such or in the form of their salts, or in the presence of substances that cause salt formation. For salt formation there may be used, for example, amonia, an alkaline substance such as an alkali metal or alkaline earth metal hydroxide, an alkali metal carbonate or bicarbonate, or a physiologically tolerated organic base. The compounds can be made up, inter alia, into preparations suitable for oral administration and lowering the blood sugar in the treatment of diabetes.

There follows a description of the results of tests on animals dealing, first, with the blood sugar lowering activity of nineteen members (tolbutamide being one) of the class in tests on rabbits, dealing next with the same activity of thirteen members (tolbutamide being one) of the class in tests on dogs and, finally, with the results of tests on humans. In this respect the specifications states as follows, the italics being intended to point out expressions which in my opinion indicate that what is being asserted is not utility for tolbutamide alone but for all the products of the alleged invention.

Clinical tests performed on a large number of patients have fully established the efficacy of the *products of the present invention,* for example, N-(4-methyl-benzene-sulphonyl)-N'-(n-butyl)-urea and N-(4-methyl-benzene-sulphonyl)-N'-isobutyl-urea, in lowering the blood sugar level. For example, the first named compound lowers the blood sugar level of healthy human beings by an average of 20-40 mg/per cent. In the case of certain diabetics a lowering, for example, of about 300 mg/per cent to the normal value of about 120 mg/per cent has been observed. *The products of the invention* have been tested as anti-diabetics in light and severe cases of diabetes mellitus. In many cases an impressive improvement in the metabolism was observed, more especially in sthenicadipose patients of advanced age. High glycosuriae and hyperclycaemiae have been normalised to a far-reaching extent, and the patients were freed from troublesome polydypsia and polyuria. In some cases the products develop their action on the very first day, and in general between the 2nd and 5th day. The reduced glycosuria is invariably accompanied by a distinct lowering of the blood sugar

[1] 65 R.P.C. 255.

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level. The renal threshold for glucose is not raised. *During the administration of the compounds* the usual diabetes diet must be strictly observed. Observations so far made show that *the compounds are effective in most,* but not in all forms of diabetes.

With some patients successfully treated for a prolonged period with *the compounds of the invention* the metabolism remains compensated for some time after the compounds have ceased to be administered and can be re-established, if necessary, by renewed administration. So far no insulin-resistance has been observed. The patients can be changed over to insulin treatment at any stage after treatment with *the compounds of the invention.* The blood count, function of the liver and the urine of the patients treated were carefully checked and displayed no pathological changes. The patients can also be treated with a combination of *the products of the invention* and insulin, whereby a saving in insulin and an improvement of the metabolism are achieved. In these cases the patients must be treated under particularly strict supervision, because the combined effects involve an increased risk of insulin shock.

The compounds of the invention may be administered in accordance with the following guiding principles, in which N-(4-methyl-benzenesulphonyl)-N'-(n-butyl) urea is used as an example.

To produce rapidly a sufficiently high blood sugar level, 2-3 grams of this compound are administered on the first day with careful checks of the metabolism. On the second day the dose is reduced to 1.5-2 grams, and on the following days 1 to 1.5 gram each are administered. In some cases the dose can be further reduced or entirely dispensed with, while keeping constant check on the sugar in the blood and in the urine. Owing to the protracted action of the compound the daily dose can be administered all at once. Higher doses do not as a rule produce an increased action.

The compounds of the invention are usually extremely well tolerated. *Their* acute *toxicity* (tested on mice or rats), as can be seen from the following Table, is between 1 and several gram/kg at an LD_{50}, for oral administration:

Next there is a table indicating the results of lethal dose tests of twelve members of the class (tolbutamide being one) on mice and of tolbutamide on rats, and the specification continues:

Tests conducted with N-(4-methyl-benzene-sulphonyl)-N'-n-butyl-urea, marked S^{34}, have shown that the blood very rapidly absorbs *the compounds* from the alimentary canal. Their discharge into the urine also occurs relatively rapidly and almost quantitatively. No detectable amounts accumulate in particular organs, and *the good tolerance of the compounds* can be attributed to this fact. Thorough pharmacological investigations, more especially with respect to muscle and liver glycogen, have shown that the lowering of the blood sugar by the compounds of the invention is not the symptom of a toxic action. Moreover, the tolerance in the endurance test, as has been demonstrated on animals by administering over a period of several months a daily dose of 100 mg/kg, *for example,* of N-(4-methyl-benzene-sulphonyl)-N'-n-butyl-urea, is very high.

Extensive clinical tests performed on numerous patients have demonstrated *the good tolerance of the compounds,* for example, N-(4-methyl-benzene-sulphonyl)-N'-n-butyl-urea and of N-(4 methyl-benzenesulphonyl)-N'-isobutyl-urea.

As compared with compounds of similar constitution of the sulphanilyl series *the compounds of the present invention* are distinguished, on one hand, in that they are more resistant to external oxidising influences, such as atmospheric oxygen, which is of importance to their shelf-life and handling, and, on the other, in that *they* have no bacteriostatic action.

Furthermore, the new compounds do not produce the secondary effects of sulphonamides on the blood (Heinz bodies) or on the thyroid gland, nor the digestive disturbances caused by action on the bacterial flora of the alimentary tract.

Next there follow, introduced by the statement "The following examples illustrate the invention", 41 examples describing methods of preparation of various members of the class. Three of these are examples of specific methods for the making of tolbutamide. In another example, forming part of a supplementary disclosure, which describes the making of a compound differing from tolbutamide only in that its right end group is an isobutyl group, it is stated tolbutamide may be similarly made. This completes the disclosure portion of the specification.

The specification then states:

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

and in the case of each of the ten patents there is a group of claims the first of which is for a process for making the same class of sulphonyl ureas, but in each case by a different chemical reaction. Claim 1 of patent 582,621 is typical and reads as follows:

1. A process for the manufacture of sulphonyl-ureas of the general formula

$$R—SO_2—NH—CO—NH—R_1$$

in which; R is a radical selected from the group consisting of phenyl, substituted phenyl having up to two substituents selected from the group consisting of alkyl-alkoxy and halogen, and aliphatic and cycloaliphatic hydrocarbon containing 3-8 carbon atoms; R_1 represents a radical selected from the group consisting of aliphatic and cycloaliphatic hydrocarbon containing 2-8 carbon atoms, and salts thereof; said process comprising reacting together compounds of the formula.

$$R—SO_2—NH_2 \text{ or its alkali salts and } R_1—NCO.$$

It is the portion of this claim commencing with the words "said process comprising reacting together" which differs from claim 1 of the other nine patents and in which they differ from each other.

It will be observed that the number of mathematically conceivable substances embraced in the class defined in this

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claim is infinite. More than one hundred substances are conceivable by taking any one of the left hand or R substituents and applying all the possible variations of the finite class defined for the right hand or R_1 group. A group many times the size of that number is also conceivable by applying it to the various substituents embraced within the finite portions of the left hand or R group. But in using the expressions "alkyl" and "alkoxy" and in embracing both single substituents in the phenyl ring in any of three positions and combinations of any two substituents in any two positions the language places no mathematical limit whatever on the number of carbon atoms or the formations thereof which such groups can have and thus makes the number of members of the class mathematically infinite. Nor is there evidence of how many members of this class are conceivable either as a matter of practical chemistry or for the purposes of practical commercial manufacture. As a matter of interpretation however it is in my opinion clear that the claim refers to every mathematically conceivable sulphonyl urea of the class for I can see no basis upon which anyone who might contrive to make a substance of the class, however inconceivable the preparation of such a substance may have been at the time of the drafting of the claim, could successfully maintain that his substance was not within the class. But even if the claim were read as referring only to those members of the class which as a matter of chemistry or even of commercial manufacture could conceivably be made, I see no reason to doubt that it would refer to a class many thousands strong. (*Vide* evidence of Professor Brown at pages 325 to 327).

I turn now to the objections to the validity of claims 1 and 10 (13 in the last) raised by the defendant in the course of the argument. A few of these objections applied to only one or two of the ten patents and in view of the conclusion I have reached it will serve no purpose either to set them out or to deal with them. The remainder applied in the same way to all ten patents. It was submitted:

(1) that there is ambiguity in the specifications as to what the invention is.

With respect to this point I have already expressed the

view that the specification purports to disclose several different inventions.

(2) that the class of sulphonyl ureas or particular members of it could be new only once and therefore could not afford unexpected utility more than once for the purpose of supporting a patent and that since it is impossible to tell on the evidence which of the ten processes was carried out first to produce members of the class, all ten patents must be treated as invalid;

(3) that as a group the compounds were not new having been disclosed by three earlier French patents, that some members of the group were not new and that it should be inferred that tolbutamide itself had in fact been made earlier and was not new at the date of the alleged invention of the patents in suit;

(4) that if on the one hand the invention as disclosed is regarded as being broad enough to include the whole class of substances it is plain that all of the substances have not been produced, but, if on the other hand the invention is regarded as embracing only the substances the preparation of which is described in the disclosure it is plainly much narrower than what is claimed and in either case the claims claim more than the inventor invented;

(5) that claim 10 (13 in the last) is invalid because

(*a*) tolbutamide was not new, for the reason mentioned in (3) above;

(*b*) the blood sugar lowering effect of tolbutamide was obvious having regard to the known substance, carbutamide, the molecule of which differs from that of tolbutamide only in having an amino, (NH_2), group in the position of the methyl, (CH_3), group on its left end; and

(*c*) claim 1 which is necessary to support it, is invalid.

(6) that claim 1 is invalid because

(*a*) it covers more than the inventor invented,

(*b*) not all the products produced by the process had novelty,

(*c*) not all products produced by the process have utility as claimed,

(*d*) it covers processes which do not work; and

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(*e*) it is ambiguous in that

(i) the word "alkyl" is of indefinite usage sometimes meaning only groups derived from the alkane series of hydrocarbons and at other times being used to include them and groups derived from the alkene and alkyne series of hydrocarbons as well; and

(ii) while meanings are defined for R_1 and R_2 in the sulphonyl-ureas produced by the process, no meaning is defined for either R or R_1 in the starting materials.

I do not find it necessary for the purposes of this judgment to deal with all of these objections as the evidence satisfies me that at least one of them, that is to say (5)(*c*) coupled with (6)(*c*), with which I shall deal, is sound and is sufficient to dispose of the action. In the case of each patent the claim sued on is a claim for the substance known as tolbutamide when made by the process of claim 1 or an obvious chemical equivalent. In each case this is a claim to which s. 41(1) of the *Patent Act* R.S.C. 1952, c. 203, applies and assuming validity in other respects such a claim can be valid only if it is accompanied by a valid process claim and is limited to the substance when produced by that process or by an obvious chemical equivalent. *Vide C. H. Boehringer Sohn v. Bell Craig Ltd.*[1] In the case of each patent therefore the validity of the claim sued on depends on the validity of claim 1.

I turn therefore to the question of the validity of the claims numbered 1. In the case of each patent the method of preparing the ureas referred to in claim 1 was not new and it is stated in the patent that many of the starting materials were already known. It was moreover admitted in the course of the trial that for the purposes of this case it could be taken that all of them were known. In this situation the principles stated by Jenkins J. in *Re May & Baker*[2] and applied by the Supreme Court of Canada in *Commissioner of Patents v. Ciba Ltd.*[3] *appear* to me to apply. In the *May & Baker* case Jenkins J. said at page 295:

> Now it seems to me that in considering this question one must begin by determining what is the character of the inventive step to which the

[1] [1963] S.C.R. 410.

[2] 65 R.P.C. 255.

[3] [1959] S.C.R. 378.

invention as claimed by the unamended specification would, if valid, have owed its validity as an invention. If I am right in the conclusions stated earlier in this judgment with regard to subject-matter, there is no inventive step, no element of discovery, merely in making new substances by known methods out of known materials.

What is indispensably necessary in order to elevate a process of this description from a mere laboratory exercise to the status of a patentable invention is the presence of some previously undiscovered useful quality in the substances produced. Assuming that the substances produced do possess some previously undiscovered useful quality, for example some remarkable value as drugs, then although the methods are known and the materials are known yet the application of those methods to those materials to produce those new substances may amount to a true invention, because of the discovery that those particular known materials when combined by those methods not merely produce those new substances but produce, in the shape of those new substances, drugs of remarkable value.

I think it necessarily follows that the identity of the materials chosen (by luck or good management) by the supposed inventor for the production of his new substances is of the essence of his invention.

Earlier in his judgment the learned Judge had said at page 281:

Before referring to this evidence, I should, I think, endeavour to state the principles on which, and limits within which, an invention consisting of the production of new substances by known methods from known materials can be supported from the point of view of subject-matter. I understand them to be these:—

(i) An invention consisting of the production of new substances from known materials by known methods cannot be held to possess subject-matter merely on the ground that the substances produced are new, for the substances produced may serve no useful purpose, in which case the inventor will have contributed nothing to the common stock of useful knowledge (the methods and materials employed being already known) or of useful materials (the substances produced being, *ex hypothesi*, useless).

(ii) Such an invention *may*, however, be held to possess subject-matter provided the substances produced are not only new but useful, though this is subject to the qualification that the substances produced must be truly new, as opposed to being merely additional members of a known series (such as the homologues) and that their useful qualities must be the inventor's own discovery as opposed to mere verification by him of previous predictions.

(iii) Even where an invention consists of the production of further members of a known series whose useful attributes have already been described or predicted, it may possess sufficient subject-matter to support a valid patent provided the somewhat stringent conditions prescribed by *Maugham, J.*, as he then was, in *I.G. Farbenindustrie A-G's Patents* (47 R.P.C. 289) as essential to the validity of a selection patent are satisfied, i.e. the patent must be based on some substantial advantage to be gained from the use of the selected members of

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the known series or family of substances, the whole (or substantially the whole) of the selected members must possess this advantage, and this advantage must be peculiar (or substantially peculiar) to the selected group.

It follows from the facts which I have mentioned with respect to the methods and starting materials and the principles so expressed that in the present case there could be no patentable invention corresponding to claim 1 of the ten patents having regard to the common knowledge of the art, and that claim 1 in each case cannot be supported as a valid claim unless all, or substantially all, members of the class of sulphonyl ureas defined in them possess some previously unknown usefulness. Even if the claim were read as embracing only those members of the class which as a matter of practical chemistry or of commercial manufacture could be made, it would still be necessary to the validity of claim 1 in each patent, for all, or substantially all, of such members to possess the utility. If this utility is not common to all, or substantially all, of the members of the class the process claimed in claim 1, consisting, as it does in the case of each of the patents, of the application of a known method to known materials or to materials having known chemical features does not represent an invention of a process at all let alone a patentable invention of a process. It may be that some members of the class of products have the necessary utility and in these cases there may well be invention both of the particular products and of the process by which particular starting materials may be used to produce them. But it is an entirely different matter to say that there is invention in a process which consists in applying a known method of reaction to a limitless class of known materials to produce an equally limitless class of expected products when all that can properly be said of such products is that some of them have utility and others, the identity of which is not known, may have it as well but that the infinite majority of the substances of the class have never been made or tested by anyone. The only statement of general application that can properly be made with respect to such a process is that in all cases the expected chemical reaction will probably occur to produce the expected product and there thus is no patentable invention involved in it, for *ex hypothesi* it is already known that the reaction will occur and the disclosure of it "contributes nothing to the common

stock of useful knowledge or of useful products". Unless therefore the unexpected utility of certain tested members of the class could, in the nature of the case, afford a foundation for a sound prediction that all or substantially all members of the class possess the utility there could be no invention whatever either of the class of products or of the process by which they may be produced. It follows that a patent claim in respect of an invention, the embodiments of which are stated to include a process for the making of a whole class of substances, when no such broad invention has been made, will purport to confer an exclusive property in something which the inventor has not invented, and since the *Patent Act* authorizes the grant of a patent only for an invention which the inventor has made such a claim will be invalid. Nor can the utility of some of the products of the class save the claim. *Vide* Jenkins, J. in *Re May & Baker et al* at page 288, lines 5 to 11.

Turning now to the question of the utility of the sulphonyl ureas of the class defined in claim 1 it was not suggested that any of these ureas has any usefulness whatever except as a blood sugar lowering substance useful in the treatment of disease requiring that particular effect. Moreover, even within this field in order to have utility in the patent sense it would be necessary for the sulphonyl ureas of the class to have some advantage over the known methods for reducing and controlling blood sugar in patients suffering from the disease. As previously mentioned, known methods of reducing blood sugar consisted of dieting, which might not be adequate, the administration of insulin, which would probably be adequate but which suffered from disadvantages arising from the method of administration by needle, and the oral administration of IPTD, which would be highly detrimental to the health of the patient and cannot therefore be regarded as a practical method at all. I mention the administration of IPTD, however, because it serves to point up that the fact that a new substance might show blood sugar lowering activity when administered orally is not by itself sufficient to warrant the conclusion that it would possess advantages over known methods of blood sugar lowering and thus be useful in the patent sense.

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In this connection reference should also be made to the question whether, at the material time, the oral administration of carbutamide was a further known method of treatment. Carbutamide had already been tested and had been put on the market in January 1956 and was thus in use for the better part of that year before tolbutamide made its appearance on the market in September 1956. Moreover, at page 18, line 13, of the patent (exhibit 2) substances of the series of which carbutamide is both a member and one which closely resembles tolbutamide in molecular structure, are mentioned for the purpose of comparison of effects. On the other hand exhibit H states that tolbutamide had been prepared and tested for toxicity and activity and tried in clinical tests before carbutamide was known. Having regard to the lengthy testing required before a substance of this kind is put on the market and to the length of time carbutamide was in use before tolbutamide made its appearance it seems to me more probable that carbutamide was discovered first and should therefore be regarded as part of the prior art, but as, on the evidence, the matter is not free from doubt I propose to omit it from consideration. The question as to utility for which I propose to seek an answer on the evidence is accordingly (paraphrasing the question posed by Jenkins, J. in *Re May & Baker et al.*[1] at page 283, lines 4 to 7): Can it be predicated of all the products of the process claim in claim 1 of each of the patents—or of substantially all of such products—that they have advantages for lowering and controlling the blood sugar level of patients suffering from diseases such as diabetes over the known methods of (1) dieting; and (2) the administration of insulin? I should add at this point, as did Jenkins, J. at page 283, line 7, that in considering the evidence on this question, it is important to distinguish between the utility of "the products of the invention" that is to say, in so far as claim 1 of each of these patents is concerned, the whole group of sulphonyl ureas included in the definition of the claim, and the utility of the specific substances of the class, including tolbutamide, which are cited as examples in the specifications or are described in the evidence. Tolbutamide and several other members of the class may well possess the necessary advantages, in fact tolbutamide

[1] 65 R.P.C. 255.

appears to have utility even if carbutamide is regarded as part of the prior art, but all that is a far cry from saying that all or substantially all members of the class have utility.

At this point I think I should say, as I did in *C. H. Boehringer Sohn v. Bell Craig Limited*[1], that while the burden of proving that the processes claimed in claim 1 of the patents in suit would not produce a whole class of useful substances as defined therein, rested on the defendants the proposition that all or substantially all of the limitless number of substances which could be produced by these processes as defined have value as oral antidiabetic medicines, when it is apparent from the mere size of the class that most of its members could never have been made or tested by anyone, is so preposterous as to require little in the way of evidence to dispel any presumption of its truth. Presumed or not the proposition shocks ones credulity.

But however that may be, it is in evidence that the pharmacological effects of new and untried substances are not generally predictable or, if predictable at all, are not predictable to any great extent. Thus there is evidence given by Professor Herbert C. Brown, a professor of chemistry of outstanding qualifications, that significant discovery generally arises largely by chance and that before any drug is introduced it must be tested upon thousands of test animals to make sure it has no undesirable effects upon the body and tissues, and only if it passes these tests does it reach the stage of clinical tests and observations to ensure that it has no undesirable effects on human functions. He also stated with respect to blood sugar lowering substances that it is not sufficient to have material which does the job of lowering the blood sugar, that in addition the material must be one which the body can tolerate for long periods of time and can use without damage to the body and that this can only be determined by extensive testing. In cross-examination he further stated, and though not himself a pharmacologist he was, in my opinion, adequately qualified so to state, that even a pharmacologist would not be able to predict the pharmacological effects of compounds which have not been made and tested. The evidence of Dr. McKendry to my

[1] [1962] Ex. C.R. 201 at 244.

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mind also substantiates the view that the usefulness of a new substance in the treatment of disease is not predictable and can only be determined after extensive testing. This generalization is I think borne out as well by the evidence of Professor Brown that between 1918 and 1926 it was discovered that three different substances of the group known as guanidines possessed some blood sugar lowering activity and that one was less toxic than the other two, but that when applied clinically over a long period liver and kidney damage resulted from its use. The generalization is I think further supported by the evidence that in the years between 1935 and 1952 following the discovery of sulfanilamide numerous substances of that family, one of which was IPTD, were synthesized and tested in the hope of finding more effective and less toxic medicinal substances, and that this was done even though it was in a sense predictable with respect to some of them that they would have bacteriostatic effects similar to those of sulfanilamide itself, but in greater or less degree. The evidence as to the testing of metahexamide and the use of carbutamide is, I think, to the same effect.

Next there is evidence that the number of substances which have been made and described by chemists amounts to about 1 million which makes it clear that the great bulk of conceivable substances embraced within the class defined in the claims have not in fact been produced or tested and that nothing is in fact known of what their pharmacological effects or usefulness may be. There is evidence that some 700 members of the class have indeed been synthesized and to some extent tested for the purpose of determining their blood sugar lowering activity but while exhibit H indicates that many of this number showed the presence of the activity in greater or less degree, apart from mentioning several members of the class of which the toxicity is regarded as low, the evidence indicates nothing as to the toxicity or undesirable side effects of most of the substances tested. It is, however, stated in exhibit H at page 450 with respect to the whole series of the class in which the R group is unsubstituted phenyl that the substances "in particular those with an n'butyl group (preparation 19154 melting point 130°-132°) have a good blood sugar lowering activity but no practical substance of particular significance

resulted from this series". The evidence of Dr. Brown at pages 253 to 255 confirms the hypoglycemic activity of the substance with no substitution on the benzene ring and with an n-butyl group on the right end i.e., N-benzene sulphonyl, N_1-n-butyl urea, but says nothing of its toxicity or side effects save that it does not have undesirable bacteriostatic activity. It also appears from the evidence that small differences in the molecules of two substances may make a great deal of difference as to whether the substance will be useful for a particular purpose or not or will exercise additional effects which are not desired. Thus the carbutamide molecule differs from the tolbutamide molecule only in having an amino rather than a methyl group at the left end but the substance exhibits undesirable bacteriostatic activity. The removal of the amino group and replacement of it by a hydrogen atom apparently eliminates the bacteriostatic activity but while the substance has good blood sugar lowering activity according to exhibit H it is not a "practical substance of particular significance". On the other hand replacing the hydrogen atom with a methyl group yields the substance known as tolbutamide which is apparently the most useful member that is known of the class. It is also worthy of note that according to exhibit H when the methyl group is present in the para position on the phenyl ring, the substances of the class exhibit no bacteriostatic activity, and the theory is that the methyl group is oxidized in the body, but the same assertion is not made with respect to members of the class having other substituents on the phenyl ring in para or other positions.

Exhibit H also states that "the results of tests show that all p-alkyl or p-alkoxy sulphonyl ureas with a suitable N_2 radical possess an exceptional blood sugar lowering activity insofar as the number of carbon atoms of the substituent in the p position does not substantially exceed 6". Considered along with the statement in the specifications that when the alkyl or alkoxy groups bound to the benzene ring are "of higher molecular weight the activity of the products is generally considerably lower", this appears to me to indicate that there are members of the class in which apart altogether from the questions of toxicity the blood sugar lowering effect itself may be zero or so small as to be useless. The claims however include

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p-alkyl and p-alkoxy groups with any number of carbon atoms.

It is also of significance that of the whole host of substances embraced in the class, up to the time of the trial, only two, tolbutamide and chlorpropamide, were in use and Dr. McKendry had heard of no others known to be useful. Had there been any known pharmacological use for any of the other products I think Dr. McKendry would have known and would have been able to tell about it and his inability to do so, satisfies me that for the great bulk of the class no such use is known.

On the whole, therefore, I am of the opinion that it is highly improbable that all, or substantially all, of the members of the infinitely large class defined in claim 1 of the ten patents have either the blood sugar lowering activity to a useful extent or the freedom from toxicity or harmful side effects necessary to render them useful and that the question which I have posed as to whether it can be predicated of all the products of the process claimed in claim 1 of each of the patents—or of substantially all of such products—that they have advantages for lowering and controlling the blood sugar level of patients suffering from diseases such as diabetes over the known methods of (1) dieting; and (2) the administration of insulin, should be answered in the negative. It follows in my opinion that there was no invention as claimed in claim 1 of each of the patents, that claim 1 in each case is accordingly invalid and that because it is invalid claim 10 of the first nine patents and claim 13 of the last patent are invalid as well.

I should add that while the objections to the patent are pleaded in a manner which I have found confusing, the objection which I have sustained is in my opinion raised, and is thus open to the defendants, by the plea that claims 1 and 10 of the first nine patents and claims 1 and 13 of the last patent are invalid for the reason that there was no invention having regard to the common knowledge of the art. As claim 10 of the first nine patents and claim 13 of the last patent are the only claims sued on, a plea in defence that claim 1 in each case was invalid is relevant, so far as I can see, only as a defence to the claim for a declaration of the validity of the patents or as a defence to the whole of the action on the ground that the claims sued

on were not supported by valid process claims as required by s. 41(1) of the *Patent Act*. The first phase of the objections which I have sustained, that is, that claim 10 in each of the first nine patents and claim 13 of the last patent are invalid because claim 1 in each case, which under s. 41(1) is necessary to support them, is invalid, is thus included in the plea and the objection to claim 1 in the case of each patent on the ground that there was no invention corresponding to it because the utility of the products, which is the essence of the invention of the process as claimed, is lacking, is the substance of the objection to claim 1 which I have held to be well founded.

In view of the conclusion which I have reached on the validity of the claims sued on it is not necessary for the purposes of this judgment that I should consider the issue of infringement and as no question of credibility arises in connection with it I do not propose to deal with it.

The action accordingly fails and it will be dismissed with costs but the plaintiffs are entitled to the costs occasioned by the defendants' motion to amend their particulars of objection and may tax and set off such costs against those recovered by the defendants.

Judgment accordingly.