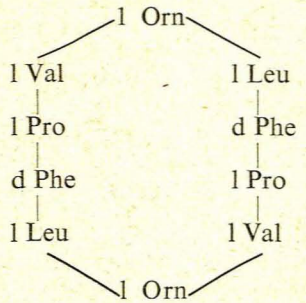
South African Medical Journal
Suid-Afrikaanse Tydskrif vir Geneeskunde

VAN DIE REDAKSIE

PEPTIED-ANTIBIOTIKA

Parallel met ondersoek na die struktuur van die polipeptiedprinsipes van die harsingslymklier,[1] vind navorsing op 'n soortgelyke grondslag plaas om die struktuur van die polipeptied-antibiotika[2] vas te stel.

Tirotrisien, die eerste bakteriese antibiotika wat verkry was (van *Bacillus brevis*), is naderhand in gramisidiene en tirosidiene geskei. Daar is getoon dat een hiervan, gramisidien-S, uit 10 aminosuur-eenhede bestaan, en die wyse waarop hulle aaneenskakel, is bekend. Daar is twee molekule elk van l-ornitien, l-valien, l-leusien, l-prolien en d-fenielalanien. Die volledige struktuur van hierdie antibiotika word as volg beskrywe.



Die struktuur van tirosidien-A en tirosidien-B is ook bekend en toon 'n groot ooreenkoms met dié van gramisidien-S. Hulle is almal ringvormige dekapeptiede, met 5 van die aminosure, in elk, identies en in dieselfde volgorde aaneengeskakel. Elkeen bevat d-fenielalanien en nie die l-isomeer nie wat gewoonlik in proteïene aanwesig is. Dit is aan die hand gedoen dat hierdie eienskap miskien die antibakteriese aktiwiteit van hierdie besondere polipeptied-antibiotika verklaar. Die ringvormige aard van die polipeptiede is nie noodsaaklik vir antibakteriese aktiwiteit nie, aangesien 'n reguitketting-dekapeptied, met dieselfde aminosuur-volgorde, gesintetiseerd is, wat 1/10de tot 1/40ste van die antibakteriese aktiwiteit van gramisidien-S[3] besit. Tirosidiene en gramisidien-S is ietwat meer ingewikkeld in struktuur as die oktapeptiede vasopressien en oksitosien.

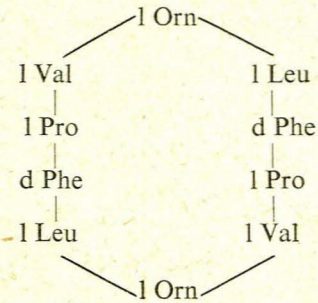
Dit kom voor asof die verskillende antibiotika wat deur *Bacillus subtilis* geproduseer word, ook polipeptiede is. Dit is bewys dat basitrasien byvoorbeeld, uit 10 verskillende polipeptiede bestaan, waarvan 3 antibakteries is. Die volledige struktuur van basitrasien-A is nog nie vasgestel nie maar die aminosuur-volgorde van 'n gedeelte van die molekuul is bekend.

EDITORIAL

PEPTIDE ANTIBIOTICS

Parallel with the investigations into the structure of the polypeptide principles of the pituitary gland,[1] work has been proceeding along similar lines to determine the constitution of the polypeptide antibiotics.[2]

Tyrothricin, the first bacterial antibiotic to be obtained (from *Bacillus brevis*) was separated subsequently into gramicidins and tyrocidines. One of these, gramicidin S, has been shown to consist of 10 amino-acid units, and the way in which they are linked together is known. There are 2 molecules each of l-ornithine, l-valine, l-leucine, l-proline and d-phenylalanine. The complete structure of this antibiotic is depicted as follows:



The structure of tyrocidine A and tyrocidine B is also known, and closely resembles that of gramicidin S. They are all cyclic decapeptides, with 5 of the amino acids in each identical and linked together in the same sequence. Each contains d-phenylalanine, not the l isomer, which is commonly present in proteins. It has been suggested that this feature may account for the antibacterial activity of these particular polypeptide antibiotics. The cyclic nature of thé polypeptides is not essential for antibacterial activity, since a straight-chain decapeptide with the same amino-acid sequence has been synthesized and found to have 1/10th to 1/40th the antibacterial activity of gramicidin S.[3] The tyrocidines and gramicidin S are somewhat more complicated in structure than the octapeptides vasopressin and oxytocin.

The several antibiotics produced by *Bacillus subtilis* appear also to be polypeptides. Bacitracin, for example, has been shown to consist of 10 different polypeptides, of which 3 have antibacterial potency. The complete structure of bacitracin A is not yet established, but the amino-acid sequence of part of the molecule is known.

The group of peptide antibiotics obtained from

Die peptied-antibiotika-groep wat van *Bacillus subtilis* verkry word, staan as polimiksiene bekend. Hulle struktuur is gedeeltelik gestaaf. Dit is getoon dat polimiksien 5 bestanddele het waarvan die vernaamste een, polimiksien-A, identies met erosporien is.

Die samestelling van ander peptiede met antibiotiese aktiwiteit word ondersoek, terwyl die sintese van sulke middele soos die reguitketting-dekapeptied, waarna hierbo verwys is, van groot belang is.

Slegs gedurende die afgelope paar jare is die pogings, om die struktuur van die polipeptiede toe te lig, geslaagd. Die metode van papierchromatografie eerder as die ouer tegnieke, het gehelp om die konstituerende aminosure makliker te skei. Verder, deur gebruik te maak van verwante metodes van navorsing, kan die volgorde van die aminosure in die ketting vasgestel word, asook hulle aard en die relatiewe getalle van elk wat in die verbinding aangetref word. Met sommige van die metodes wat in hierdie studies gebruik is, word die end-aminosuur uitgeken; sekere van hierdie metodes stel navorsers in staat om die polipeptied trapsgewyse af te breek. Deur middel van papierchromatografie is die produkte van parsiële hidrolise van volledige polipeptied-antibiotika al van mekaar geskei; die kolletjies op die papier word afsonderlik ge-eludeer, dan word die di- en tripeptiede heeltemal gehidroliseer en die aminosure word deur verdere papierchromatografie[2] geïdentifiseer. Waar die polipeptied by ondersoek nie vry is van peptied-onsuiwerhede nie, moet ander metodes gebruik word. Een van die metodes wat vandag algemeen gebruik word om die polipeptiede van mekaar te skei, is dié van teenstroomverdeling: die mengsel word agtereenvolgens in 'n spesiale apparaat verdeel wat 'n oplossingsvloeistof-fase en 'n waterfase bevat; daar is 'n aantal buise so gerangskik dat komponente met 'n hoë oplosmiddel/water-verdelingskoëffisiënt by die een en tvan die apparaat bymekaar kom en dié met 'n lae verdelingskoëffisiënt by die ander ent. Tirotrisien was deur hierdie metode in verskeie verwante polipeptiede gefraksioneer. Papierelektroforese is nog 'n metode wat gebruik word om verwante polipeptiede van mekaar te skei.

Deur gebruik te maak van die nuwer en meer aantreklike tegnieke wat dit moontlik maak om stowwe te skei en te ontleed sonder om hulle unieke en labiele strukture te versteur, het navorsing i.v.m. polipeptiede die afgelope jare vinnig gevorder.

1. Van die Redaksie (1955): S. Afr. T. Geneesk., **29**, 697.
2. Robinson, F. A. (1956): J. Pharm. Pharmacol., **8**, 297.
3. Erlanger, B. F. en Goode, L. (1954): Nature, **174**, 840.

Bacillus polymyxa are known as polymyxins. Their structure is partly established. Polymyxin has been shown to have 5 constituents, of which the main one, polymyxin A, is identical with aerosporin.

The structure of other peptides having antibiotic activity is being investigated, while the synthesis of such agents as the straight-chain decapeptide to which reference is made above, is of great interest.

It is only in the last few years that attempts to elucidate the structure of polypeptides have been successful. The method of paper chromatography has enabled the constituent amino-acids to be separated more easily than by the older techniques. Furthermore, by the use of related methods of investigation the sequence of the amino acids in the chain can be determined, as well as their nature and the relative numbers of each present in the compound. Among the methods that have been used in these studies are some in which the terminal amino-acid is identified; certain of the methods permit stepwise degradation of the polypeptide to be effected. By paper chromatography the products of partial hydrolysis of complete polypeptide antibiotics have been separated from one another; the spots on the paper are separately eluted, the di- and tri- peptides then hydrolysed completely, and the amino acids identified by further paper chromatography.[2] Where the polypeptide under investigation is not free from peptide impurities other methods must be employed. One that is widely used at present, to separate polypeptides from one another, is the method of countercurrent distribution, in which the mixture is successively partitioned in a special apparatus containing a solvent phase and an aqueous phase; there are a number of tubes so arranged that components with a higher solvent water partition-coefficient collect at one end of the apparatus and those with a low partition-coefficient accumulate at the other end. By this method tyrothricin was fractionated into several related polypeptides. Paper electrophoresis is another method used to separate related polypeptides from one another.

The investigation of polypeptides has advanced rapidly in recent years through the application of the newer elegant techniques which make it possible to separate and analyse substances without disturbing their unique and labile structures.

1. Editorial (1955): S. Afr. Med. J., **29**, 697.
2. Robinson, F. A. (1956): J. Pharm. Pharmacol., **8**, 297.
3. Erlanger, B. F. and Goode, L. (1954): Nature, **174**, 840.