"Collagen"

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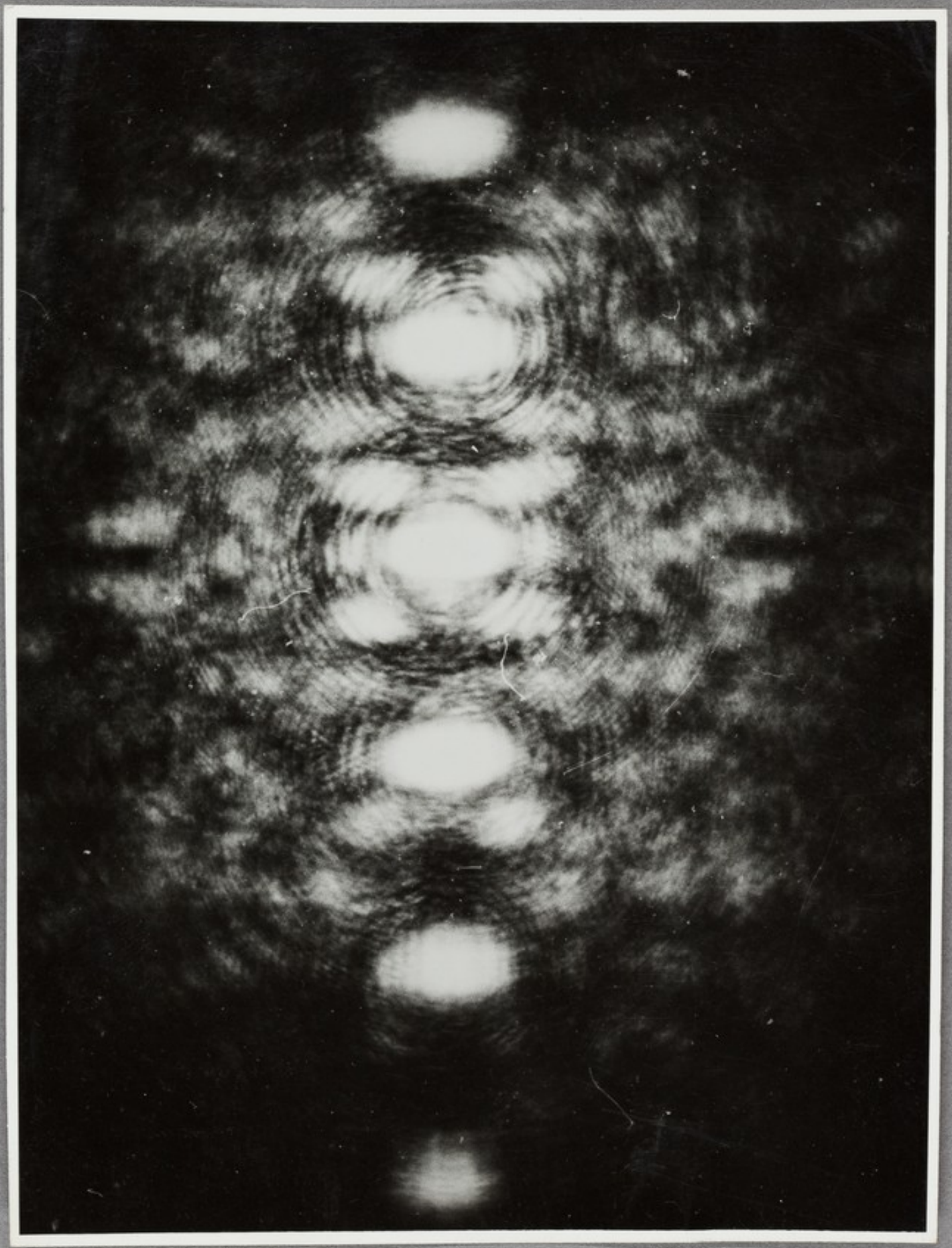
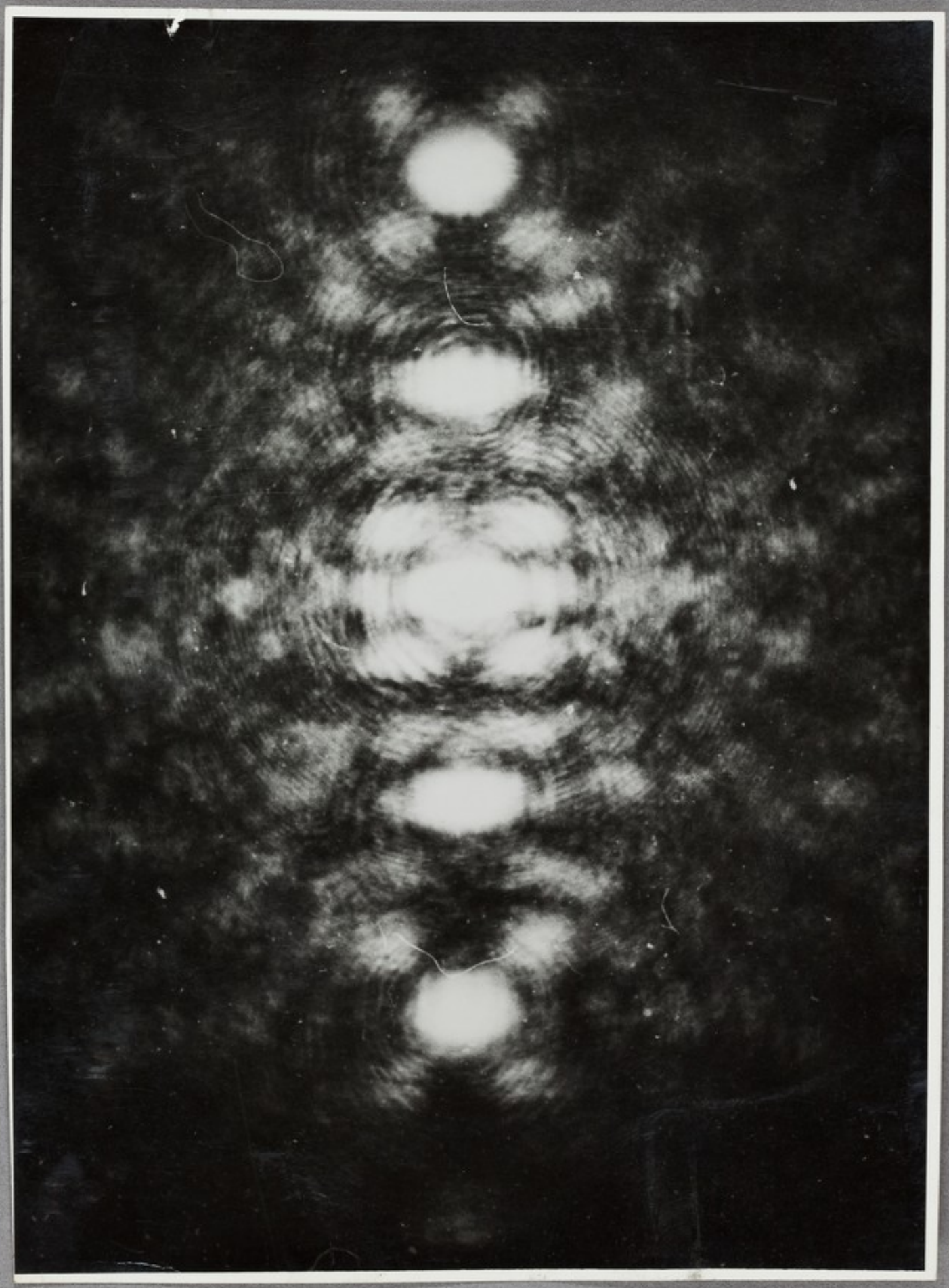


Crude Collagen

1) main drain without protein



Crude Collagen

7). main chain + proline 1 in 2

UNIVERSITY OF LONDON KING'S COLLEGE.

From The Wheatstone Professor of Physics,
J. T. RANDALL, F.R.S.

TEMPLE BAR 5651
(6 LINES).

STRAND. W.C.2.

Dr. F.H.C. Crick,
Polytechnic Institute of Brooklyn,
The Protein Structure Project,
55 Johnson Street, 4th Floor,
Brooklyn 1, New York

17th June 1954

Dear Crick,

Thank you for your letter of June 3rd. We have been working away at the collagen structure and, like you, regret that the complete answer is so elusive. I don't wish to go into any great detail here as much of our work will be presented at the Society for Experimental Biology Symposium at Leeds in September and in my Procter Memorial lecture in the same month. This latter I expect to be published in October, some long time before the Symposium is in print I imagine.

However, I should like to summarise a few important points from our conclusions about your model:

1. We also have noted that the dichroism expected for your proposed model does not correspond with that observed.

2. Although we have not yet calculated it, we think that your structure would have negative birefringence, not positive as observed.

3. The density for hexagonal packing, assuming an average side chain, is 1.8. While you point out that your structure may contain only the smaller side chains and therefore be only part of the collagen fibre, it seems rather unlikely that alternate residues are glycine as you suggest. It is even more unlikely that it should be polyglycylproline, although this is of course not necessary.

4. Points 1 and 2 may of course also be got round if, as seems likely, the collagen system is not simple but consists of two "phases".

5. The number of close contacts might be expected to make the structure unstable.

6. The main chain radius, being rather large, one might expect packing difficulties unless only the smaller side chains are involved.

7. Enclosed are two enlargements of optical diffraction patterns: (1) contains all main-chain atoms, but no side chains, while (2) has main-chain atoms and alternate residues proline.

As you can see, there is a reasonably good general resemblance to the X-ray

diffraction diagram, particularly in case (2). There are two serious points of discrepancy: (a) The meridional 2.95A reflection is too strong; this is more obvious on the actual negative. (b) The equatorial layer does not fit at all well, maxima coming where there should be minima and vice versa.

We have calculated the equatorial form factors with and without proline and have tried the effect of adding other side chain atoms. The calculated form factors do not account for the observed relative intensity changes on swelling. The $11\bar{2}0$ reflection expected for hexagonal packing, which is not observed, would occur at a position of larger F^2(calc.) than that of the observed $20\bar{2}0$ reflection. Similarly, as stated above, the observed minimum on the equator is not given by the form factor. One reaches the general conclusion that the radius of the helix is too large.

The effects of forming super-helices of various radii were also investigated. While it is possible to choose a radius which will produce a minimum at the desired place, there does not seem to be any particularly good physical reason for assuming this radius. In any case, a definite minimum of scattered intensity is still observed for stretched fibres. Further, the most likely super-helix for your structure to assume from packing considerations would have seven residues per minor turn and the ratio of the meridional spacings 9.55/2.86 should be 3.5 and not 3.33 (i.e. $3\frac{1}{3}$ which fits in better with a three chain model).

Yours sincerely,

J.T.Randall. FRS

COLLAGEN

The structure of collagen has recently been reviewed by Bear.[1] Since then, Dr. P.M. Cowan and her co-workers in Professor J.T. Randall's Laboratory at King's College, London, have obtained an improved wide-angle X-ray diffraction photograph, which strongly suggests that the structure is helical. (This photograph was shown in March, 1953, at a Faraday Society Meeting. The details of it are not available to me). In spite of this important advance, no satisfactory structure has yet been proposed.

Bear[1] has argued that the bands and interbands of collagen seen in the electron microscope may have different amino acid compositions, and in particular that the more ordered interbands may contain predominantly the shorter amino acids. If this were so, then it would be possible in the interbands to accommodate four residues in every stretch of 2·9 Å in the fibre direction, instead of the three normally assumed. The model proposed here has been constructed on this basis, and therefore applies only to part of the collagen molecule.

The model consists of two polypeptide chains wound helically round a common axis. The backbones of these chains are related by a diad coinciding with the fibre axis. The asymmetric unit consists of two residues, which will be called A and B.

All the peptide links have the cis configuration. The planes of successive peptide links on either chain are alternately perpendicular and parallel (approximately) to the fibre axis, as shown in figs 1 and 2 respectively. The two chains are held together by hydrogen bonds perpendicular to the fibre axis, and passing quite close to it (fig. 1). The pairs of peptide groups thus linked together form sheets of atoms perpendicular to the fibre axis and 2·95 Å apart, and they therefore contribute strongly to the meridional reflections. These sheets are linked by the other, alternate, peptide groups of the polypeptide chains, as shown in fig. 2.

There are ~~no~~ two distinct structures of this general type. One has

a right-handed helix, and has a close van der Waals contact between Cα (B) and N(A). The other has a left-handed helix, and has a close contact between Cα (A) and O (B). The latter accommodates proline more easily, and is the one for which details are given here. The left-handed screw axis of the helix has been given a translation of 2.95 Å and a rotation of 55°. This represents a slightly extended form of the molecule. The wide-angle X-ray diagram normally observed[1] probably corresponds to a somewhat distorted helix.

Approximate cylindrical coordinates for the structure are given in Table 1. They should not be regarded as final. Because of the short van der Waals contact, several of the angles have been distorted by a few degrees from their most likely values.

The model imposes certain restrictions on the side-chains. Residues of type B cannot be proline or hydroxyproline; those of type A may be. There is a close approach between the β carbon atom of a residue of type B on one chain and that of the nearest residue of type A on the other chain, which suggests that one member of any such pair will be glycine. This would account for the high glycine content of collagen.

The structure appears to be in qualitative agreement with the X-ray data, but in view of its unusual features it must be considered tentative until a more careful comparison has been made with experiment.

I should like to thank Dr. Thomas Furnas, Jr., for allowing me to study his unpublished X-ray photographs of collagen, and my colleagues at the Protein Structure Project for helpful discussion.

F.H.C. Crick

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[1] R.S. Bear. Ad. in Protein Chem. Vol. VII, 1952, Academic Press. Pages 69-160.

LEGENDS and FIGURES

Fig. 1. A section of the structure perpendicular to the fibre axis at z=0 as the plane ~~z=0~~. A and B denote the two types of residue. Hydrogen bonds are shown dotted. DOWN and UP show the general run of the polypeptide chains. The arrow represents the direction of the projection shown in fig.2.

Fig. 2. A projection of part of one chain of the structure, ~~perpendicular to the fibre axis, and~~ in the direction shown by the arrow in fig. 1. The vertical arrow is the fibre axis. The small arrow represents the general run of the helix. The two horizontal lines represent two of the planes of atoms, separated by 2.95 Å, of the type shown in fig. 1. The residue of type A has been shown as proline; that of type B as alanine.

TABLE I

Approximate cylindrical co-ordinates

Atom	R (Å)	θ	z (Å)
	Residue A		
Cα	3·55	0°	0·0
C	2·05	+1·5°	0·0
O	1·65	-36°	0·0
N	4·3	-15°	+0·8
(Cβ)	4·1	-4·5°	-1·4
(Cγ)	5·4	-14°	-1·35
(Cδ)	5·25	-23°	-0·1
	Residue B		
Cα	3·3	- 4°	+2·95
C	4·3	-17°	+2·15
O	5·2	-24°	+2·7
N	1·9	-14°	+2·95
(Cβ)	3·9	- 6·5°	+4·35

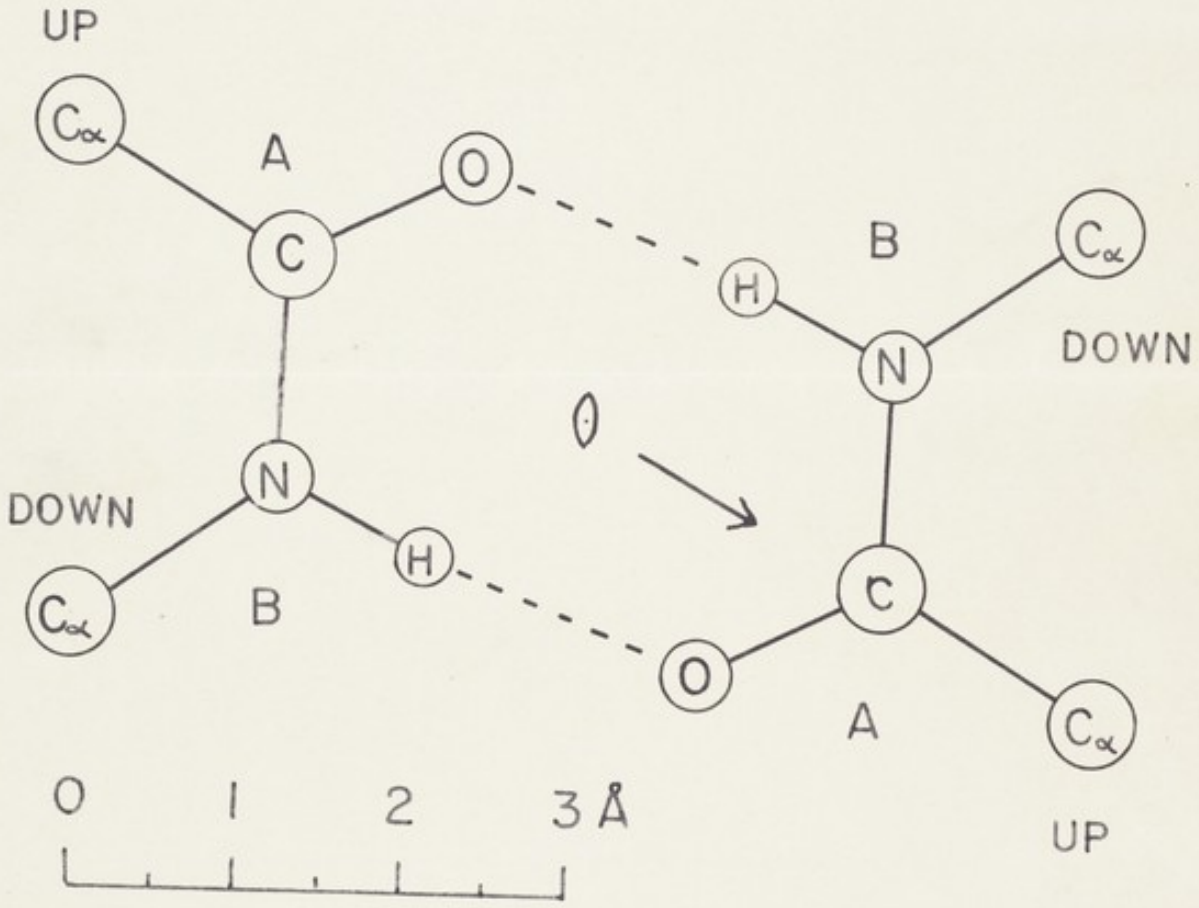


Fig1

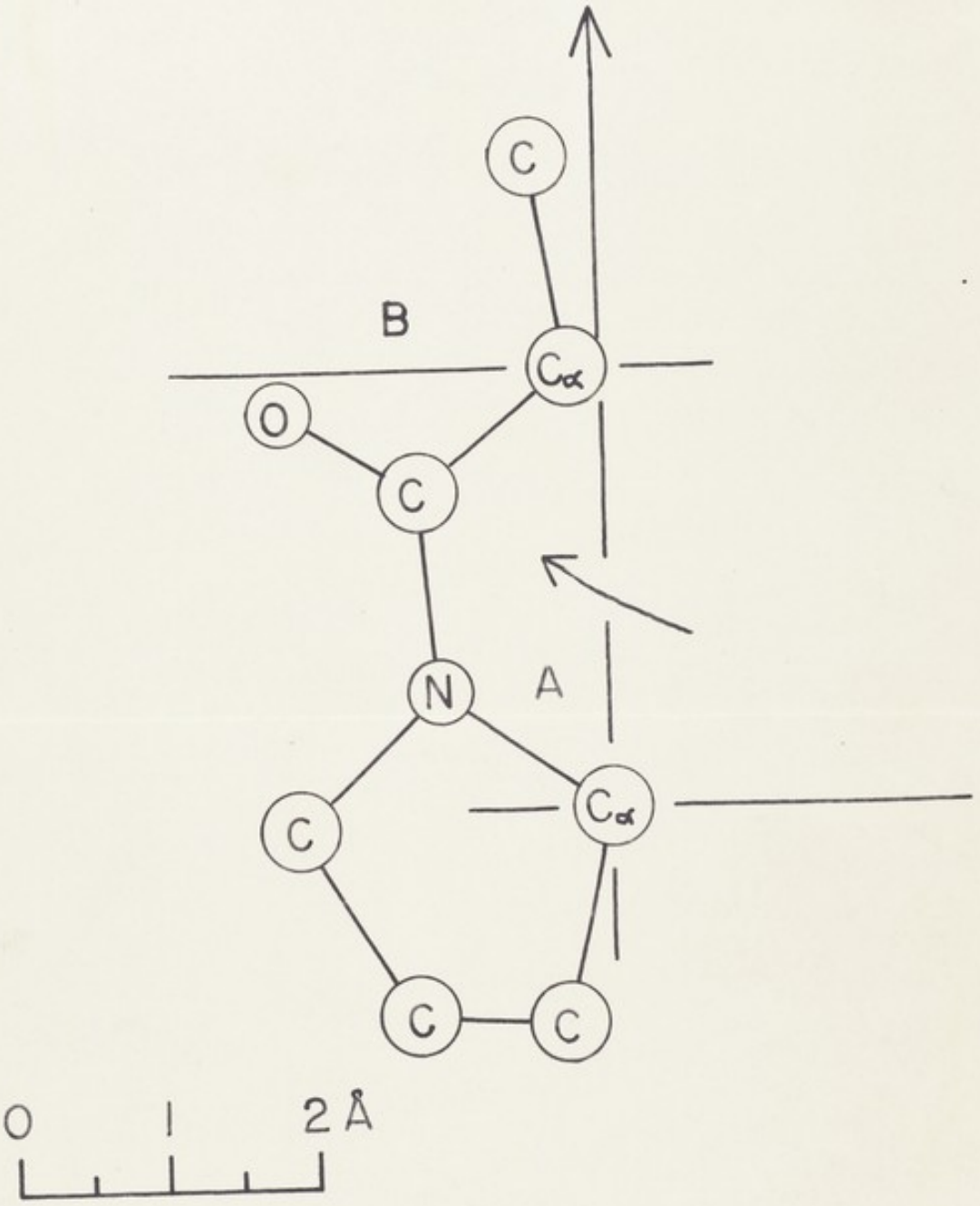


Fig 2

final few words.

to what does it do?

protein synthesis

:

Gamow's scheme :- almost certainly wrong:

"Ultimate" aim: to make DNA replication happen in the test-tube. NOT SYNTHESIS FROM SCRATCH

to take system apart, purify it, and then put it together again.

models suggest ideas how to do this.

but

The man who gets the $64,000

is the one who does it.

Notes

10^6

$e^2 \sim 7$

$e^5 \sim 10^2$

$e^{15} \sim 10^6$ ~ 15 × 500

10 kilo

Accuracy

Lebland work
-Powell

worming-over

Diethyl formamide. ⇌ ⟹

+ o
− o

− o
+ o

10
o

o
+ o

10
•

− o
− o

o +
o +

+ o
o

5 cm/H°.
÷5 to get 1 cm/H°.

$\frac{1}{2}$ cm/H°.

1 cm/H°.

$\frac{1}{4}$

(+)
+
o
o

−
o

40÷5=18

Pure no 5 in 2 chloroform
Pure no 4 " 3 " "
Pure no 3 " 4 " "
Pure no 2 " 5 " "

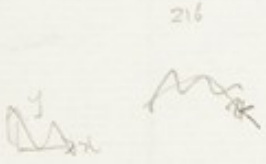
Hypo

CR r = 14.3 cm

4.6 / 14.3 = .322 ϕ = 18.8°

sin ϕ = x/r

x



216

5 cms / 11°

1 cm / 11° : x 2/10

-16

-108

-124°

180

(56°) sin 56° = .829

-.829

-13.1

-216

-16

-232

180

sin +52° = .788

+12.5

108

5

536

360

176

10

73

324

16

340

+20

+8.8

432

16

448

360

-88

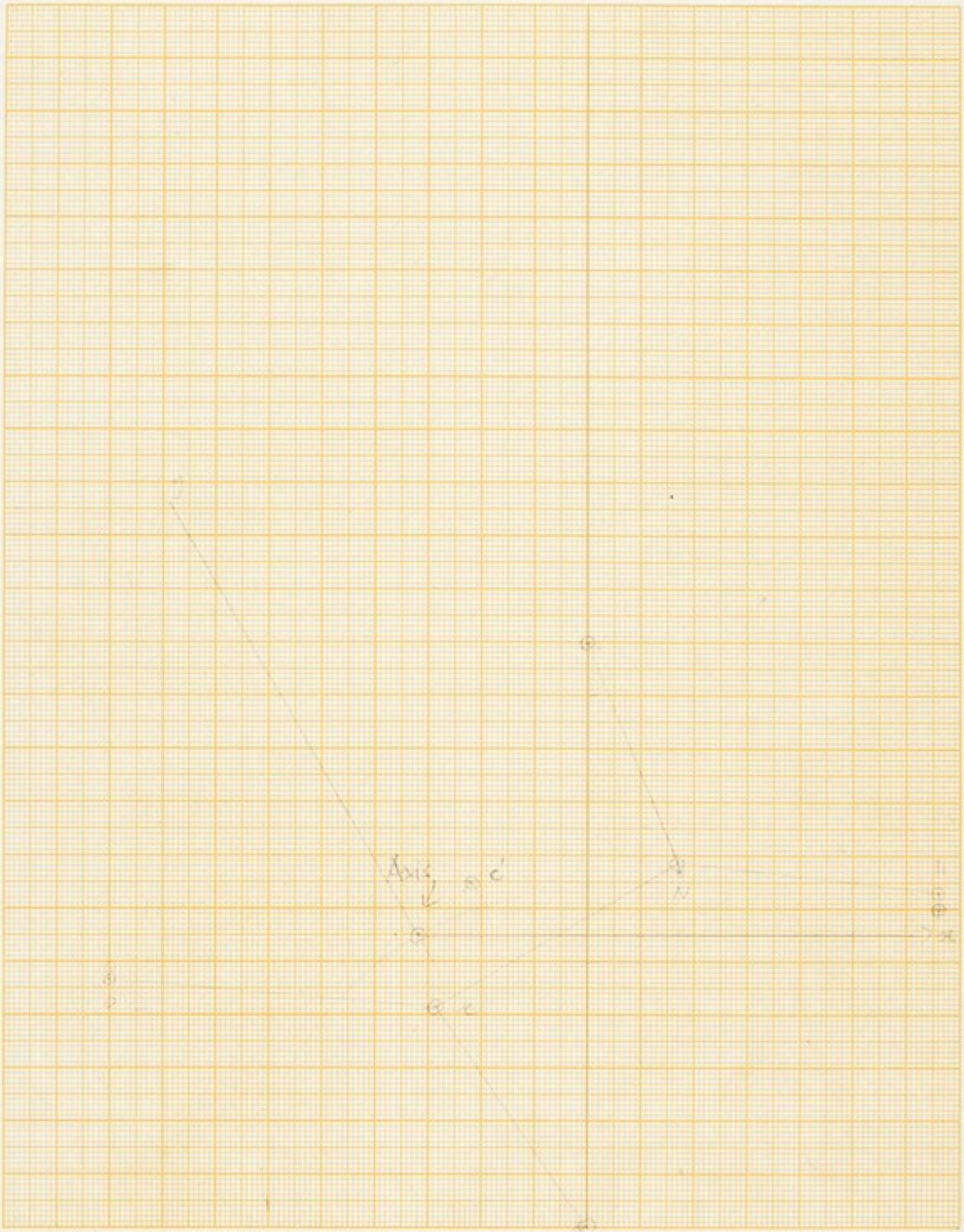
516

96

-216

+34°

.559



page 2 Echos reckoned.

Fig 1 Bones thickness.

Table 1

page 4 B angle.

Fig 2. Manuel's picture.

p. 8. physiochem. reckoned.

Fig 3. Manuel put picture.

2.68
2.79
2.80
2.80
2.81
2.81
2.81
2.83
2.84
2.85
2.87
2.87
2.88
2.89
2.90
2.93
2.93
2.94
2.97
2.99
2.99
3.00
3.00
3.03
3.04
3.04
3.07
3.07
3.10
3.11
3.14
3.17