October 28, 1941

D r a f t

It may be worthwhile to attempt to observe the 24-minute period above the background of the natural beta activity without any chemical separation except a removal of the natural beta active products of uranium after irradiation. Data obtained by Anderson and Fermi show that there is a residue of beta activity which apparently cannot be removed by repeated ether extractions. Whether or not the 24-minute period would be observable above this background depends on the value of the radiative capture cross-section which at present is not known. The following question arises in this connection: Is it not possible that this residual beta activity which is observed after repeated ether extractions is due to internal conversion electrons from an excited U134 into which UX may decay by means of two beta transformations corresponding to the branch which has a probability of .3%? If such an excited U134 were responsible and if it had a lifetime of a day or so, the residual beta activity might be removed by making successive ether extractions at intervals of one or two days.

Apart from using photo neutrons from beryllium for these experiments, it is proposed also to use photo neutrons which have been slowed down by carbon, parrafin or lead in order to measure the ratio of radiative capture and fission in the neighborhood of 50,000, 10,000 and 5,000 volts.

The question of the balance of the slowing down process and fission in the region of two million volts is in the meantime receiving continued attention. In 1939 when this question was first discussed most of those interested in nuclear physics took it for granted that uranium was slowed down two million volt neutrons with a cross-section of about 4×10^{-24}. Experimental physicists believed that nuclear theory predicted that all heavy elements slow down neutrons very strongly, whereas theoretical physicists believed that this was an experimental fact. In the discussion which took place with Dr. Roberts and Dr. Abelson in connection with the meeting on October 21, 1939, Dr. Wigner, Dr. Teller and I emphasized the view that there is no evidence which would allow to predict whether or not uranium would efficiently slow down neutrons of energies between one and four million volts. Either Abelson or Roberts suggested thereupon that in experiments along this line a uranium fission chamber should be used as indicator for the neutrons. Dr. Zinn and I started experiments along this line in February, 1941. These experiments show that lead and bismuth have a very small cross-section for slowing down D + D neutrons below the fission threshold of U238. The experiment has also been performed for uranium, but no final conclusion has been reached because the particular uranium sample which we used became pyroforic, and it became, therefore, impossible to analyze it for moisture or oxygen. A new batch of uranium metal has been under order for some time, and the experiment will be repeated with this new batch.

L. Szilard
January 18, 1943

We can write the critical condition for a fast neutron chain reaction in ordinary uranium as follows:

$$\frac{\sigma_f^*}{\sigma_f^* + \sigma_n^*} \nu^* q^* + \left(1 - \frac{\sigma_f^*}{\sigma_f^* + \sigma_n^*}\right) y \nu^{235} = 1 \qquad (1)$$

Or neglecting fission in 235 (y = 0) we can write

$$\frac{\sigma_f^*}{\sigma_f^* + \sigma_n^*} \nu^* q^* \cong 1 \qquad (2)$$

In this equation, y tells us what fraction of those fission neutrons which have been slowed down below the threshold of U238, will cause fission in 235; q*, is the fraction of the fission neutrons which have at the time of their emission, energies above the threshold of 238. σ_f^* and σ_n^* signify the average fission cross section of U238 for those of the fission neutrons which have an energy above the threshold of 238. Thus, $\sigma_f^* \cdot f^*$ means the average fission cross section in 238 for all fission neutrons. ν^* is the number of neutrons emitted by 238 fission caused by fission neutrons. The same letters without the stars will be used for the corresponding values for neutrons from Ra-Be sources.

An experiment performed with Ra-Be neutrons on a uranium sphere of 10 cm diameter, showed that a Ra-Be source in the center of the sphere increased the total number of neutrons by a factor of about 1.15. The same sphere caused a reduction of the fast fission count in a fission chamber by a factor of .675. Assuming $\nu = 2.5$, we may say that 0.25 fission neutrons have been created while ~~and leaving~~ 0.9 of the original Ra-Be neutrons, survive but ~~and~~ a certain fraction of these has been slowed down below the threshold of 238.

If we neglect the fact that we have $q^* \sigma_f^* \neq q \sigma_f$ and also disregard that a fraction of the 0.15 excess neutrons created in the uranium sphere is also slowed down by the uranium sphere, we may write for the fraction of the surviving Ra-Be neutrons which have been slowed down below the threshold of 238,

$1 - .675 + 0.15 = ~~.525~~ .475$

We may conclude that if all the Ra-Be neutrons which survive and were originally capable of causing fission in 238 had been slowed down in a larger mass of uranium, we would have obtained in the first generation

$$0.25 \times \frac{0.9}{.975} \quad 0.470$$

fission neutrons.

We may therefore write

$$0.47 = \frac{\sigma_f}{\sigma_f + \sigma_n} q \nu \qquad (3)$$

or dividing No. 2 with No. 3, and putting $\nu = \nu^*$

we obtain

$$\frac{1}{.47} \cong 2.1 = \frac{\sigma_f^* q^*}{\sigma_f q} \cdot \frac{\sigma_f + \sigma_n}{\sigma_f^* + \sigma_n^*} \qquad (4)$$

If we now assume that $\sigma_f^* = \sigma_f$; $q = \frac{2}{3}$ / $q^* = 4/5$

and further assume that 4/5 of the fission neutrons are at birth above the threshold of 238, and 2/3 of the Ra-Be neutrons are at birth above the threshold of 238, i.e.: $q^* = \frac{4}{5}$, $q = \frac{2}{3}$

then we obtain from (4)

$$\frac{\sigma_f + \sigma_n}{\sigma_f^* + \sigma_n} = 1.75 \qquad (5)$$

This means that the chain reaction would go with fast neutrons in 238. For instance, for the following set of values :

$\sigma_n = 2.7$ / $\sigma_n^* = 1.25$; $\sigma_f = \sigma_f^* = 0.7$

if on the other hand, we assume $\varphi = 1/2$

then, we obtain:

$$\frac{\sigma_f + \sigma_n}{\sigma_f^* + \sigma_n^*} = 1.4$$

and this means that the chain reaction would go for the following set of values: $\sigma_n = 2.7$, $\sigma_n^* = 1.7$; $\sigma_f = \sigma_f^* = 0.7$

for $\nu = 2$ we obtain $\varphi = 2/3$

$$\frac{\sigma_f + \sigma_n}{\sigma_f^* + \sigma_n^*} = 1.57$$

which is consistent with the following set of values: $\sigma_n = 2.7$, $\sigma_n^* = 1.5$, $\sigma_f = \sigma_f^* = 0.7$

3b,s-10

L. Szilard
January 18, 1943

We can write the critical condition for a fast neutron chain reaction in ordinary uranium, as follows:

(1) $$1 = \frac{\sigma_f^*}{\sigma_f^* + \sigma_n^*}\nu^* + \left(1 - \frac{\sigma_f^*}{\sigma_f^* + \sigma_n^*}\right) y\, 2.2$$

or

(2) $$1 \cong$$

neglecting fission in 235

In this equation, y tells us what fraction of those fission neutrons which have been slowed down below the threshold of U238, will cause fission in 235; q^*, is the fraction of the fission neutrons which have at the time of their emission, energies above the threshold of 238. σ_f^* and σ_n^* signify the average fission cross section of U238 for those of the fission neutrons which have an energy above the threshold of 238. Thus, $\sigma_f^* \cdot q^*$ means the average fission cross section in 238 for all fission neutrons. ν^* is the number of number of neutrons emitted by 238 fission caused by fission neutrons. The same letters without the stars will be used for the corresponding values for neutrons from Ra-Be sources. ~~of Ra-Be neutrons.~~

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For the average cross section of Ra-Be neutrons for fission, Fermi and Anderson have given the value of .45, whereas, Marshall and Szilard find for the average cross section of fission neutrons (originating from fission in 235) an average cross section of 1/3 of 1.3/2.2 = .6. If we assume that about ~~30%~~ of the Ra-Be neutrons is below the threshold of 238, we can write for σ_f ~~=~~ 0.45 3/2 = 0.7

and if we assume that about 1/5 of the fission neutrons have energies below the fission threshold, then we may write for σ_f^* ~~also~~ about ~~1.5.~~ 0.75

Putting in these values we see that the chain reaction would go in pure uranium 238 if the inelastic cross section for Ra-Be neutrons would be about ..... and for fission neutrons, would be about .

Ans. I

Neglecting that $q^*\sigma_f^* \neq q\sigma_f$ ~~and~~ (but also neglecting the slowing down of fission neutrons we may ~~0.67~~ write for the ~~one~~ fraction of the above threshold neutrons which have been slowed down

$$1 - .675 + 0.15 = .525$$

Ans II

We may therefore write

$$0.\cancel{48} = \frac{\sigma_f}{\sigma_f + \sigma_n} \nu q$$ or dividing Nσ with these and

~~by introducing this in to N σ(2) and neglecting the fission for n < 2~~ ~~(q = 0)~~ putting $\nu = \nu^*$

$$\frac{0.525}{\sigma_f - \nu q} = \frac{\sigma_f^*}{\sigma_f^* + \sigma_n^*} q^* \nu^*$$

$$\frac{\sigma_f + \sigma_n}{\nu = \nu^*}$$

$$\text{or } 0.525 = \frac{q^* \sigma_f^*}{q \sigma_f} \sigma_f + \sigma$$

$$\frac{1}{0.450} = \frac{\sigma_f^* q^*}{\sigma_f q} \frac{\sigma_f + \sigma_n}{\sigma_f^* + \sigma_n^*} = 2.20$$

$$\frac{0.6}{0.45} = 2.6 = 3.17$$

$$\frac{\sigma_f + \sigma_n}{\sigma_f^* + \sigma_n^*} = 1.43$$

$$\frac{\sigma_f^* + \sigma_n^*}{0.75} = 1.5 = 2.25 = 1.41$$

CP and CF Report

L. Szilard
January 25, 1943

In order to see whether a fast neutron chain reaction can be maintained in ordinary uranium, we have measured the fast neutron fission counts by means of a fission chamber outside of a uranium pile while a Ra+Be neutron source was placed somewhere near the center of the pile. If a fast neutron chain reaction can be maintained in uranium, and if we gradually increase the size of the pile, we should eventually reach a size at which the fast neutron fission count outside the pile begins to rise above the value which would correspond to the inverse square law in the absence of uranium. For piles up to 4 tons we found the fission count fell was falling with the increasing mass, and fell to about 1/20 for a 4 ton pile. At that size it fell roughly to 1/3, and a layer of about 4 cm thickness was added to the pile so as to bring up the mass to 4 tons. We cannot conclude from the recent results without going into a detailed consideration of the phenomena involved that a chain reaction cannot be maintained in ordinary uranium. We cannot exclude the possibility for an exceedingly large size uranium pile. Corresponding to the migration length of neutrons which are below the fission threshold of U238 and which might not be slowed down except by elastic collisions, The migration length for causing fission in U^{238} is very large. It is however, without detailed theory, evident from our observation that the fast neutron chain reaction cannot be maintained in piles of a few hundred tons of weight.

Insert in Section V, after first sentence:

Elements which are in the periodic table in the region of bismuth and having an atomic number above 81 have a low absorption for slow neutrons and do not slow down appreciably fission neutrons. For this reason they are suitable as a cooling agent and can be used for cooling along internal surfaces within the lattice element. Liquid bismuth, liquid alloys of bismuth, and lead, and liquid lead can thus be used as cooling agent. Bismuth is more favorable from the point of view of slow neutron absorption than lead, and the liquid bismuth alloys occupy a position in between according to their composition.

Heavy water

The example shown in figure 3 is adapted for replacing graphite by heavy water as the slowing agent. The aluminum tube, no. 3, in figure 3 separates the heavy water used as a slowing agent from the cooling agent which flows into the gap between the aluminum tubes, 2 and 3. Heavy water itself can be used as a cooling agent in place of ordinary water. The cylindrical uranium rod, no. 1, in figure 3 can be replaced by a cluster of uranium rods such as the cluster shown in figure 42. These uranium rods may be coated with aluminum if heavy water is used as a cooling agent.

repeat Fig 3
under new number!

May 21, 1943

SECTION 5A

Beryllium

Uranium spheres surrounded with a layer of beryllium or cylindrical uranium rods surrounded with a cylindrical layer of beryllium, may be used as lattice elements in a lattice which is embedded in graphite of heavy water. Spheres of uranium metal, 5 cm. in diameter, surrounded by a $2\frac{1}{2}$ cm. layer of beryllium metal are, for instance, an example of the lattice element which can be used in graphite to be in the potentially chain reacting unit. An example for a lattice element in which a cylindrical rod of uranium is surrounded with a layer of beryllium is shown in Fig. 80.

July 23, 1943
L. Szilard

In my letters to Fermi in July 1939, and also in A-55, I disclosed a method for determining a length A which is characteristic for a system in which the thermal neutron density obeys the diffusion equation. This method consists in measuring the thermal neutron density along a closed surface at one point in the interior of the space which is enclosed by the said closed surface. The thermal neutron density is then reduced to 0 along the closed surface by introducing cadmium, and the thermal neutron density is again measured at the said point in the interior.

By applying this method to a chain reacting mixture, one can determine the critical dimensions of a sphere by multiplying the length A with π and at the Washington meeting in June 1940, Fermi explicitly proposed the use of this principle for determining the critical dimensions. The specific form in which Fermi proposed to try this principle is at present called an exponential experiment, and Fermi gave a short description of the exponential experiment which he proposed at the Washington meeting in June 1940. The same exponential experiment has been actually performed by Fermi in April 1940 for the purpose of determing the length A in the limiting case when we had pure graphite that did not contain any uranium.

August 5, 1944

There has been lately much talk about the organization of our work in peacetime, about such questions as the publication of the results obtained during the war and peacetime application of our discoveries. Some physicists and chemists who may be considered as key men in this work have been offered postwar positions by various firms that want to get into this new field after the war and one of these men has actually accepted such a position. The situation is such that it seems to me very desirable that we should try to agree on a common line of basic policy which could be followed individually and, if necessary, collectively.

The purpose of this letter is to find out whether there is sufficient agreement among us on certain basic principles to formulate such a common policy. I shall in the following therefore record those of my beliefs which I hope I share with the majority of our group and I would very much appreciate it if you would comment on these points and indicate your disagreement wherever you disagree.

1. The "modern" development with which we are all familiar makes it impossible to ensure peace on the basis of the Wilsonian ideas, which are essentially characterized by the slogans of cooperation between sovereign states bound together by covenants possibly reinforced by alliances, definition of the aggressor, and compulsory collective action against the aggressor. Those ideas might have been effective after the last war if they had been acted upon at that time but if after this war

we have an armed peace in which a number of nations are in possession of "modern" weapons and if one of these nations starts a war, that war may be over in 24 hours and there will be no time to apply whatever definition of an aggressor has been formulated. If after this war we get an armed peace based on balance of power of several states in possession of the "modern" weapons then we physicists must regard that era as a pre-war rather than a postwar period. Judging from newspaper reports it is such and armed peace, at best along Wilsonian lines, towards which we are drifting.

In order to ensure peace we must now insist that the "modern" weapons be overwhelmingly in the hands of one single closely knit group, either the United States alone or the United States and Great Britain tied together by an indissoluble alliance approaching some sort of a union or some larger group possibly embracing even the whole "civilized" world, but in any case a group which forms a much closer union than can be achieved by political treaties uniting sovereign nations. If such a group's domination is based on the quantity and quality of modern weapons which it has accumulated and if they safeguard this supremacy by policing the whole of the world so that any danger to security can be met by police action rather than by war, then perhaps we might consider that state of affairs as peace and return to our peacetime pursuits. That it takes more than controlling all the deposits and policing the world to ensure a lasting peace is self-evident, but the level on which this additional question has so far generally discussed is hardly adequate and therefore I do not believe that the time is right for us to try to formulate a collective opinion.

It is not entirely out of the question that the physicists and chemists who are engaged in this work will have to consider it their duty to raise their voices against the postwar world organization towards which we are drifting at present. We can of course not foresee how this war will go on. It may be that tomorrow's newspaper will report the use of "modern" weapons by the Germans on Cherbourg, London, or Manhattan. If that happens our eloquence could not compete with the eloquence of events and there would be no need for us to raise our voices.

On the other hand, it may well happen that the postwar world organization will begin to take shape in Europe before the full meaning of the development of modern weapons has dawned upon the world and in that case we might perform an exceedingly important function by exerting an influence individually or collectively in favor of what we believe to be a necessary political development. I can even visualize a situation where we would want to visit personally Congressmen and Senators or other key men in Washington in support of a policy of the administration which is resisted by those politicians who were not given enough time fully to understand the implications of the modern development. It may very well be that such an activity on our part may not remain without effect, for politicians, whatever ~~xhxx~~ other shortcomings they may have, are usually shrewd judges of human nature and they will have no difficulty in seeing that we are sincere and have no political axe to grind.

~~The first~~ One question about which we ought to reach an agreement is thus whether or not we are willing to take our share of responsibility in influencing political action if circumstances arise in which this appears desirable. To a certain extent ?

2. It seems to me that as long as the danger exists that we are moving towards a balance of power and in the absence of a police, by far the most important peacetime application of the modern development will remain the maintenance of peace.

It seems to follow that in such a situation we cannot think of returning to the normal method of publications which would make basic information available to the future enemy. Clearly we have to steer clear of two dangers: One, to have no secrecy at all and give away the information to the enemy and, the other, is to hinder the work of our own physicists and chemists by preventing them from freely discussing their results with each other. If we do the former, countries which start from scratch can catch up with us and surpass us within two or three years. If we do the latter, it may take a country starting from scratch somewhat longer to accumulate the basic information needed for this work, but if they trust their own men they will be in a much better position with respect to unrecognized problems and therefore in the long run (say 5 to 10 years) far better off than we are. It follows that we have a difficult task (1) to persuade our politically less interested physicists to cooperate in a scheme of withholding information from everybody who does not take responsibility to keep this information from leaking out, and (2) to make it clear to the authorities that a large group of scientists freely communicating information to each other is a minor danger to security but that the existence of such a group is essential to arrive at a balanced judgment as to which lines ought to be supported and also essential to attain that research spirit without which we cannot hope successfully to compete with other countries.

As to what is secret it seems to me that we should take the stand that the most important secrets are the basic information, the points of view which we consider ought to be guiding, and the emphasis which we wish to put on one of the other line of development. Once this information is available to any country which wishes to start from scratch the mere constructional problems can be solved in an incredibly short time by a capable group of engineers.

3. The question arises as to whether this development is best carried out under Government auspices or under other institutions where the profit object plays no role or whether industrial research laboratories are more suitable for a speedy development. If we restrict ourselves to basic research and that very important technological and designing work which carries the development from its early beginnings into the process designing stage I believe that it would be best to keep these branches of the work out of the hands of commercial companies. It is quite true that our experience with government run enterprise has been most unfortunate, but there is no law of nature which says that a government run organization must necessarily be badly run. I believe that if we could make our advice heard we could put forward proposals for a number of organizations, all of them in the last analysis controlled in some form by the Government, which could operate with elasticity of small private firms. It seems to me therefore that we should not give up the hope that Government controlled organizations could satisfactorily carry on this development after the war until we have made a real effort to obtain a form of organization which we consider satisfactory.

As far as pure research is concerned and a considerable fraction of the effort ought to go into pure research carried out in the best of academic tradition, it may be that a decentralization at various universities might be of value. However, I believe that we must watch out that the desires of various universities to acquire modern instruments should not be allowed to become the guiding principle of this decentralization.

2. It seems to me that as long as the danger exists that we are moving towards a balance of power and in the absence of a police, by far the most important peacetime application of the modern development will remain the maintenance of peace. Bus 3

It seems to follow that in such a situation we cannot think of returning to the normal method of publications which would make basic information available to the future enemy. Clearly we have to steer clear of two dangers: One, to have no secrecy at all and give away the information to the enemy and, the other, is to hinder the work of our own physicists and chemists by preventing them from freely discussing their results with each other. If we do the former, countries which start from scratch can catch up with us and surpass us within two or three years. If we do the latter, it may take a country starting from scratch somewhat longer to accumulate the basic information needed for this work, but if they trust their own men they will be in a much better position with respect to unrecognized problems and therefore in the long run (say 5 to 10 years) far better off than we are. It follows that we have a difficult task (1) to persuade our politically less interested physicists to cooperate in a scheme of withholding information from everybody who does not take responsibility to keep this information from leaking out, and (2) to make it clear to the authorities that a large group of scientists freely communicating information to each other is a minor danger to security but that the existence of such a group is essential to arrive at a balanced judgment as to which lines ought to be supported and also essential to attain that research spirit without which we cannot hope successfully to compete with other countries.

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As far as pure research is concerned and a considerable fraction of the effort ought to go into pure research carried out in the best of academic tradition, it may be that a decentralization at various universities might be of value. However, I believe that we must watch out that the desires of various universities to acquire modern instruments should not be allowed to become the guiding principle of this decentralization.

August 10, 1944

There has been lately much talk about the organization of our work in peacetime, about such questions as the publication of the results obtained during the war and peacetime application of our discoveries. Some physicists and chemists who may be considered as key men in this work have been offered postwar positions by various firms that want to get into this new field after the war and one of these men has actually accepted such a position. The situation is such that it seems to me very desirable that we should try to agree on a common line of basic policy which could be followed individually and, if necessary, collectively.

The purpose of this letter is to find out whether there is sufficient agreement among us on certain basic principles to formulate such a common policy. I shall in the following therefore record those of my beliefs which I hope I share with the majority of our group and I would very much appreciate it if you would comment on these points and indicate ~~your disagreement wherever you disagree.~~ Before the end of the next 2

1. The "modern" development with which we are all familiar will make it impossible to ensure peace on the basis of ideas which date back to 1918 and are essentially characterized by the slogans of cooperation between sovereign states bound together by covenants possibly reinforced by alliances and automatic collective action against nations. Those ideas might have been effective after the last war if they had been acted upon at that time but if after this war we have an armed peace in which a number of nations are in possession of

"modern weapons and if one of these nations starts a war, that war may be won in 24 hours and there will be no time to apply sanctions. If after this war we get an armed peace based on balance of power of several states in possession of the "modern" weapons then we physicists will have to regard that era as a pre-war rather than a postwar period. Judging from newspaper reports it is such an armed peace at best stabilized by alliances and league of nation covenants towards which we are drifting.

It is not entirely out of the question that the physicists and chemists who are engaged in this work will have to raise their voices against the postwar world organization towards which we are drifting at present. Of course it may be that one of these days newspaper headlines will announce the use of "modern" weapons by the Germans on Cherbourg, London, or New York, and if that should happen there may be an abrupt change in the present trend and it may not take any explaining by the physicists to make statesmen understand the situation which the world faces.

Insert I

On the other hand it may also happen that the postwar organization of the world will begin to take shape in Europe before the full meaning of the development of modern weapons has become manifest. In that case the physicists and chemists might perform a useful function by explaining in the right place and at the proper time the grave consequences to which the modern discoveries will lead if we drift into an armed peace. We may take action individually or collectively. As far as collective action is concerned it seems that we can not very well go farther than to state as clearly as we can the necessary conditions for safeguarding peace in face of this modern development. One such condition would appear to be that all pertinent deposits be controlled by one single group. If this is to be effective it will require in a sense policing of the whole world so that any danger to security arising out of the violation of the control measures could be met by police action against the administration of the territory which is involved rather than by waging war against the people who happen to inhabit that territory. As to the question of what kind of group could exercise such control it is hardly possible to give an answer. Theoretically speaking this group could be the United States alone or the United States and Great Britain, if tied together by an indissoluble alliance approaching some sort of a lasting political union. It could be the United States, Great Britain and Russia if it were possible to create an atmosphere in which a lasting union of these countries can be established. It could be some sort of a league of nations if it were possible to convince the nations to give up the idea of sovereignty to the

extent ~~that it would be~~ needed to ~~form a lasting union.~~ Any ~~such~~ measures which we could name as necessary conditions for peace are clearly not sufficient and ~~obviously~~ it takes more than such measures to create a peace in which we may have confidence. Unfortunately the public discussions of this topic have not yet reached a sufficiently high level and I believe therefore that it would be premature for us to try to reach a consensus of opinion on this subject in general.

I believe that most of us would agree that the hopes that we shall in fact get a satisfactory organization of the world after this war are slim and that even if the United States Government had a clear determination in this respect and even if the people of the United States were backing the Government 100% in this attempt, it might still not be possible to obtain such a world organization in view of the attitude which the other countries might take. In spite of this hope being slim, it would I believe be necessary at least to make an attempt in this direction.

The first question which arises then is this: Do we feel responsible for, at the proper place and proper time, putting forward our views to the extent of making clear the necessary conditions for maintaining peace in the face of the present development? Obviously some allowances will have to be made for future developments and there is hardly anybody in a better position to appreciate the importance of this aspect than our group. Are we willing if necessary to go as far as seeing personally men in key positions in Washington and also seeing Senators and Congressmen if need be,

Insert, p. 5

It seems to me that

If the present trend continues we will end up with some sort of a balance of power in the postwar world. Cooperation between sovereign states bound together by alliances, covenants stipulating collective action against aggressor nations and such other measures as were proposed at the end of the last war for the organization of the peace have been made obsolete by the "modern development" of which "our" group of physicists and chemists are aware.

Clearly if other nations who might consider themselves as our potential enemies will be in possession of modern weapons and in the absence of an overwhelming superiority of these weapons by the United States, one of these nations might, for fear or any other reason, decide to strike and win its war within a few hours before the United States or any of its Allies can think of applying sanctions. This country with its long coastlines is particularly vulnerable. The modern weapons can be smuggled in during peacetime by the agents of a "friendly" power as a purely routine precautionary measure. They will be stored in all major cities possibly over a long period of years until in an international conflict it is decided to detonate them in order to be on the safe side.

If after this war we have an armed peace in which a number of nations are in possession of modern weapons in substantial quantity and if one of these nations starts a "war" there may be no time to apply sanctions before most of the major cities in this country have been destroyed.

It is of course possible that the present trend towards such an armed peace may be changed. For one, the war is not over yet and

for all we know the Germans may use modern weapons in it before long. Their effect being demonstrated the discussion of the postwar organization might then be taken up again and carried on a level which takes into account these new realities. But even so, I fear that the chances for a stable peace after this war are slim, seeing that it takes time for people to grasp the full meaning of this new development.

For this reason we ought to proceed on the assumption that only an overwhelming superiority of this country, perhaps in collaboration with Great Britain, in the quantity and quality of modern weapons can safeguard peace.

The maintenance of the peace then is by far the most important peace application of the modern development and it is difficult to think of any other peace application which might achieve comparable importance.

It seems to follow that in such a situation we cannot think

in support of such policies of the administration which might be opposed by those who were not given enough time fully to understand the implications of the developments of which our group of physicists and chemists has been fully aware for the last three years. It appears to me conceivable that a lobby of this unprecedented type might not remain without effect because politicians are usually shrewd and would have no difficulty in seeing that we are sincere and have no political axe to grind.

~~No other peace application can compare in any way in importance.~~

2. It seems to me that as long as the danger exists that we are moving towards a balance of power and in the absence of a police, by far the most important peacetime application of the modern development will remain the maintenance of peace.

No other peace application can compare in any way in importance. The only strong argument in favor of looking for other peace applications is the possibility that certain peace applications might supply as a by-product those substances which are needed for producing modern weapons. However, I know of only one application which meets this requirement.

It seems to follow that in such a situation we cannot think of returning to the normal method of publications which would make basic information available to the potential enemy. Clearly we have to steer clear of two dangers: One, to have no secrecy at all and give away the information to the enemy and, the other, is to hinder the work of our own physicists and chemists by preventing them from freely discussing their results with each other. If we do the former, countries

Insert, p. 6

Unless we have a large group of scientists free from compartmentalization it will not be possible to attain that research spirit which is essential if we want to go after the unrecognized problems and thus ~~successfully compete~~ keep ahead with the other countries. ~~Without such a group it is not~~ possible to arrive at the balanced judgments which are needed for steering this work along the right channels. While this point will be elaborated further below, it should be emphasized from the start that compartmentalization of information as it has been practised in our projects is uncompatible with efficient development in the post-war period.

which start from scratch can catch up with us and surpass us within two or three years. If we do the latter, it may take a country starting from scratch somewhat longer to accumulate the basic information needed for this work, but if they trust their own men they will be in a much better position with respect to unrecognized problems and therefore in the long run (say 5 to 10 years) far better off than we are. It follows that we have a difficult task (1) to persuade our politically less interested physicists to cooperate in a scheme of withholding information from everybody who does not take responsibility to keep this information from leaking out, and (2) to make it clear to the authorities that a large group of scientists freely communicating information to each other is a minor danger to security but that the existence of such a group is essential ~~to arrive at a~~ balanced ~~judgement as to which lines ought to be supported and also essential to attain that research spirit without which we cannot hope successfully to compete with other countries.~~

As to what is secret ~~xxxxxxx~~ from the potential enemy it seems to me that we should take the stand that the most important secrets are the basic information, the points of view which we consider ought to be guiding, and the emphasis which we wish to put on one or the other line of development. Once this information is ~~available~~ to any country which wishes to start from scratch ~~the~~ mere construc-tional problems can be solved in an astonishing/short time by a ~~capable group of ingeneers~~. Keeping a secret from our potential enemies is, however, a very different proposition from keeping in-

formation from ourselves. While this point will be elaborated further below, it should be emphasized now that compartmentalization of information as it has been practised in certain war projects is incompatible with the efficient development work in the postwar period.

3. The question arises as to whether this development is best carried out under Government auspices or under other institutions where the profit object plays no role or whether industrial research laboratories are more suitable for a speedy development. In examining this question we shall restrict ourselves to fundamental research and that very important region between fundamental research and actual consturctional work which consists of a balanced mixture of technological development and designing work and which carries the development from the early discoveries into the process design stage. I personally believe that this part of the development work is best kept out of the hands of commercial companies provided that certain essential requirements can be met if the guidance of the work is in public rather than in private hands.

Clearly the two most important dangers of having this work go on in the postwar period under the guidance of the Government or some other public non-profit organization are the following: (1) Overcentralization. This leads to the danger that all the work will be planned work. That is, certain steering committees or administrative heads decide the relative importance of different lines of work and set up a priority system. The result is that if a group wishes to move in a certain direction because it feels that

that direction is promising at an early stage when the justification of that work cannot yet be objectively demonstrated, their work is so slowed down by having a low priority that it is practically impossible for the group to get through the preliminary stage of the work and reach the stage where they could ask for permission and high priority.

The remedy seems to lie in giving all members of the staff who have in the past proved that they are able to select promising lines of development a definite status which would enable them to proceed as follows: Something like 80% of the facilities will be subject to the priority system, that is, will essentially be reserved for planned work. The remaining 20% of the facilities can be used by any of these "fellows" if they in their group are willing to put in time along a certain line of development they will have the 20% of the facilities for whatever they think is useful work. If much such free work is going on there will be some competition for the 20% of the facilities and the free work will be somewhat slow but still it will not be completely suppressed as it is bound to be under a priority system. Another danger of the centralization is the difficulty to form temas which comprise physicists, chemists, engineers, metallurgists, etc. There may be a tendency to form a vertical organization by setting up divisions for these different categories and expecting any working group to turn for help to these divisions. There is of course no objection to having a metallurgist - etc as a service division upon which groups can call for further help

by each ~~group~~ major group will have to have its own physicists, chemists, metallurgists, etc., if it is desired to move fast through various early stages of development.

~~(2) Another danger is~~

A third danger of centralization consists in giving certain outstanding physicists or chemists the responsibility for a too large fraction of the total work. The whole machinery under one man will then essentially be dominated by the ideas of that one man and ~~it~~ that is hardly the best way for speedy progress.

~~Decentralization~~ This danger is somewhat milder of several labs under

(2) Decentralization.--Decentralization can become a very serious danger if the fact that a number of independent units are kept working in the field ~~is~~ leads to a situation when the members of one unit cannot freely discuss their work with members of another unit. The result would be that a number of problems will remain unrecognized and therefore unsolved. Apart from compartmentalization of information which would have this effect, the same effect can also be brought about if the geographic location of the various research and development units is such that it becomes very difficult for the members to have extensive talks with each other.

(3) Stuffed-shirt Direction.--In an enterprise which is carried on by the Government or some large non-profit organization the directors (administrative hands) of the organization do not participate in any financial gain or loss. This may easily lead to a situation where their chief desire is to maintain a ~~clean~~ good record as to their conduct of affairs. That is, they will desire to take action on the basis of recommendations made by certain

committees. Their desire will be to have these committees composed of men whose names are publicly known in most cases on account of some outstanding achievement in the more or less remote past. Such men are mostly rather busy, can devote only a small fraction of their time and attention to the problems involved, and have in many cases gathered their experience in a field entirely different from this field of modern development. What they know about this modern development they do not know through their own work but through what they have been told. To know what one is told is certainly not enough and it is impossible to have confidence in the recommendations of any such groups.

The sanctioning of any program of this type is probably unavoidable if we operate under Government sponsorship or large non-profit foundations. The effect of this mode of operation could however be made probably fairly satisfactory if these committees were guided in their recommendation by the recommendations of teams formed by men who have first-hand knowledge of the problems which are actually involved. I believe, therefore, that perhaps a plan of the following sort might be a workable solution;

The men in responsible scientific or technical positions (as distinct from the men in administrative positions) who have first-hand knowledge of the problems involved may be made to form a panel. It their task to keep informed as well as they can with all developments in any of the branches of this work thereby cutting across the organizational boundaries of different enterprises which make the totality of the modern development. Most men on this panel will

most of the time be fully engaged in some specific work but a fraction of them will for a certain period of time free themselves from the special work in hand and form ~~a team~~ that will from time to time go on record with respect to the overall project and the special projects which are a part of it. The composition of this team will change ~~from time to time~~, some of the members going back to special work and being replaced by other persons from the panel. It will be the task ~~of this~~ team to realize ahead of time, months or years ahead, what major issues may come up for discussion. Next they would have to take steps to get all the experimental evidence which is needed in order to give sound advice with respect to the decision. ~~Their task in this respect will be facilitated because~~ they will be free to have direct contact with those men in the special projects from whom they believe they can obtain the special information which they need. If the information is not available they will ~~have~~ to arrange for further experiments ~~to be conducted~~ to provide this information.

If this team is then put into a position to gather the necessary evidence they would have to discuss with each other the issues involved. During such a discussion it would gradually turn out that some of them have thought more about the issue than some others and in many cases the decision will end with a unanimous opinion among those who consider themselves competent to judge, while the rest will abstain from expressing an opinion as it ought to. In other cases there may be a majority opinion and a dissenting opinion (since occasionally it is unavoidable that on the basis of different experience in the past some

persons will favor one solution and some persons will favor another one).

The result of the deliberation of such a team would then go on record and would be ~~placed at the disposal of those who are in key positions and would be~~ communicated to those who have administrative positions in the various projects which compose this development, and also to the various other levels who are part of the machinery of the "modern development". —

Internal or external Criticism. —

SUMMARY

The inclosed letter is sent to those physicists and chemists upon whose discoveries, inventions, initiative, and correct judgment most of the processes of our present work ~~is~~ are based. It puts down those considerations and opinions which I believe might be shared by the majority of this group. The purpose of this memorandum is to find out whether we can reach a consensus of opinion concerning the following questions:

1. Do we feel responsible for the consequences of our work to the extent that we are willing to raise our voices at the proper time and proper place in order to give expression to our belief that the "modern" development with which we are associated will make it impossible to preserve peace which is based on a balance of power or covenants calling for collective action against aggressor nations?

2. As long as we have no organization of the peace that we can trust to be lasting it must be our concern to have in the United States an overwhelming superiority of modern weapons so as to avoid a balance of power in the field of modern weapons. Are we then willing, after the war and until such time as an adequate organization of peace is put into effect, ~~willing~~ to take a stand in favor of safeguarding the information which we have accumulated from reaching countries which are potential enemies?

3. Can we state clearly principles which will permit a sufficient safeguard of secrecy without hampering the development

work either directly or indirectly by annoying the physicists and chemists?

4. Can this work be carried on under government auspices or under auspices of other non-profit making organizations without giving up too much of the advantages of free research?

5. To what extent should there be planning and to what extent should the research be free?

6.) = 1

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(1) T2 r^+ and T4r (or some other similar combination) is mixed with bacteria in such proportions that an infection with three virus particles be ten times less probable than an infection with two virus particles. Out of this mixture after suitable dilution, about a 0.2 cc. is pipetted into a large number of small test tubes. The dilution is so chosen* as to have a probability of ~~[illegible]~~ 10% to have in one test tube two infected bacteria. All these test tubes are incubated to give one burst and then plated out in Hershey agar.

The majority of these plates will show bursts from single infected bacteria and we ~~might~~ may have an equal or larger number of plates which show bursts from two infected bacteria or bursts from mixed infected bacteria. As a first selection, we pick those plates which show an approximately equal number of large and small plaques. Taking one such plate, we dip a needle in succession into the large plaques (the original T4) and transfer the virus from them into one test tube which we inoculate with bacteria and incubate. We plate out the virus which has grown in this test tube on B and on B/4. If we find an appreciable fraction of plaques capable of developing on B/4 we conclude that the plate which we picked originates from a burst resulting from a mixed infection with exchange of character. We then retain this plate for further experiments, making either one or two sub-cultures from every plaque on the plate. These sub-cultures will then be individually analyzed to show whether they are T2 or T4 and whether they are small or large plaque formers.

Before starting this experiment, we ought to consider whether it would not be wiser to use T4 and T6 in place of T2 and T4. One of the guiding considerations should be maximum plating efficiency of the virus as used. This is essential since we want to find a correlation between the loss of the r character by one virus and the gain of the r character by the other.

Lh.

* Better use greater dilution(!) to reduce probability of two infected bacteria in one test tube to 1:50.

I. Introduction

From the tentative work of Arrhenius and Madsen[1] up until modern research, which dates from the introduction of microdeterminations in immunochemistry by Heidelberger and Kendall[22], ~~one has~~ WE HAVE searched for a method to describe quantitative reactions between antigen and antibody based on the law of mass action. Interest is not only of giving to these reactions their place in the framework of general chemistry. The knowledge of equilibrium constants and other thermodynamic quantities is a source of information which is often not replaceable by any other.

This information is at least of two types. One concerns the identification of antibody. In the actual chemical state, these proteins can only be characterized by their reaction with the opposite antigen. But the verification of inequalities in the energy of reaction allow distinction to be established between the antibody which combines specifically with a like antigen ~~but different~~ AND between those ~~by the~~ WHILE DIFFER BY details of more or less fine structure.

Another sort of information concerns the nature itself of the structures causing the union of antigen and antibody. Thanks to the development of theoretical chemistry, currently can be calculated with more or less rigor, the energy of combinations according to the type of forces set in action, that is to say, ~~finally beginning with some~~ DETERMINED BY details of structure. Reciprocally, some information on these structures ~~spin~~ ARISES from some known energy. When one has seen enough ~~of~~ reaction or HAS altered the protein molecules, this method of approach, in order to know the composition and configuration of the active groups has so much more value than a few other methods used ~~in order~~ to obtain it. Pauling[48] has opened that pertinent path of combination of antibody with antigen. However, in a thermodynamic study, it is ~~practically~~ ABSOLUTELY necessary to be able to obtain the basic known ~~enemy~~ ENERGY. The direct determination, by colorimetry of the

heat of formation of an antigen-antibody complex, has been effected only one time by Boyd and his collaborators[5]. There does not exist any analogous work on other complexes.

Finally, the only knowledge up to the present time on the forces implicated in immunological reactions results exclusively from equilibrium studies.

A convergence is imposed, with the point of view of specificity ~~with~~ OF enzymatic reactions. But the analogy cannot be carried too far. Some peculiar difficulties are encountered in the study of immunological reaction. There is, first of all, the heterogeneity of the immune serum. On the other hand, the complex found between enzyme and substrate arises generally from the union of three molecules at most, the specific protein reacting most often at non-interchangeable sites. In the antigen antibody combinations, the situation is less simple. Not only the antigen carries a relatively large number of reactive groups on its molecule from which results a variety of combinations with antibody, but the latter, if it is also multivalent, associates between it the molecules of antigen, creating agglomeration in regions of diverse composition.

For these reasons, it has appeared advantagous in this review to group the diverse immunological reactions according to the more or ~~less large simplicity of the laws which they represent.~~ BISICALLY SIMPLE LAWS WHICH THEY REPRESENT

II. Agglutinations

A. Fundamental Concepts

1. Hypothesis of the mechanism.

When ~~one has mixed~~ WE MIX a specific antiserum with a suspension of bacteria or red cells, one can expect to find a simple relation between the concentration of the agglutinin remaining free at equilibrium and the quantity of that antibody which is fixed on the cells. Two types of theories are offered in order to explain

agglutination. Bordet[2] admits that the presence of antibody renders the cellular surface sensitive to the action of electrophytes. The changes in the polar properties of the surface may also be able to have an effect. Boyd[4] has largely exposed that which perhaps could be said in favor of these conceptions. Another mechanism is suggested by the views of Marrack[39] on the formation of specific precipitates. The same forces which unite the antigen to antibody are responsible for aggregation. The antibody is then at least bivalent since it is able to unite two antigenic groups in order to form an aggregate. This point of view is in particular that of Heidelberger[20] and of Pauling[50]. The application of the law of mass action constitutes a certainly difficult problem according as one or the other type of mechanism is taken into consideration. The reason for it is only if the antibody is multivalent, the number of groups of antibody and antigen combined can only be deduced from the simple difference between the total antibody present and that which remains free at the end of the reaction. However, when there is agglutination, one has completely in place of these thoughts, for geometric reasons, the fact that the number of molecules of agglutinin effectively adhering to two cells is negligible by relation to the number of molecules simply fixed by a single group. One can then easily apply the mass action law to the fixation of agglutinins. It will suffice to treat the cell as an enormous molecule carrying a large number of reactive groups, in parts of the agglutinogen groups.

2. Laws of multiple combinations without polymerization

Let us consider a large molecule G carrying reactive group, G all alike of which each one can fix reversibly one ion or one monovalent molecule A. In the system in equilibrium with A, there exists some molecules G, GA, GA_n, GA_m having fixed 0, 1, n, m molecules A conforming to the equilibrium:

$$GA_{n-1} + A \rightleftharpoons GA_n$$

From which a series of equilibrium constants

$$K_n = (GA_n)/(GA_{n-1})(A)$$

the terms between parenthesis represent, following the custom, the activities, being, with a certain approximation, the concentration of the constituents at equilibrium.

A statistical method allows the distribution of the combined groups to be known. These are $m!/n!(m-n)!$ types of complexes. GA_n which one will designate by $GA_{n,1}$, $GA_{n,2}$... $GA_{n,i}$, $GA_{n,j}$, and are different by the sites to which are fixed the n molecules A. Let us admit only all the groups G are equivalent and that there is no attraction or repulsion exercised on the A molecules by the GA groups already combined. Then a single constant will correspond to the equilibrium between one type $GA_{n,i}$ and one type $GA_{n-1,j}$, which are n, i and j.

If one progressively increases (G) it, up until all the fixed A is fixed to obtaining G, by a sequence of such equilibria, one sees we have;

$$(GA_n) = \frac{m!}{n!\,(m-n)!} K^n (G)(A)^n$$

K is called intrinsic constant of combination of the molecule A with a group G. In making the sum of molecules A fixed by all the complexes GA_n, n varients of 1 to m, one finds that the relation of the number of groups combined GA to the total number of large molecules G present is:

$$r = \frac{mK(A)}{1 + K(A)} \qquad (1)$$

Another important concept is the degree of advancement of the reaction. That is the fraction of combined groups:

$$p = \frac{(GA)}{(G) + (GA)} = \frac{K(A)}{1 + K(A)} \qquad (2)$$

The relation between the intrinsic constants and the ordinary equilibrium constant are easy to establish. One conceives, moreover, almost all the energies of combination have been supposed equal, that the constants $K_1, K_2 \cdots K_n$ are different only among themselves by the contribution of the effects of entropy. One has:

$$K_1 = mK, \quad K_n = \frac{m-n+1}{n} K, \quad K_m = \frac{1}{m} K$$

The intrinsic constant can be considered as the constant of equilibration

$$K = \frac{(CA)}{(G)(A)} \qquad (3)$$

of the reaction $G + A \rightleftharpoons GA$ where the group G, in place of being dependent on a large molecule, would be independent of those same molecules.

One finds again in the relation (1) of isotherm adsorption of Langmuir where m is interpreted as the total number of sites of which the large molecule G has available in order to fix to its surface an A molecule.

According to the hypothesis which has served to establish that relation, one of its conditions for validity is that all the sites offered to A are equivalent. If this is not so, either on the same molecule or from one molecule to another, that is to say, if the total surface is heterogeneous, the adsorption will be represented by a Freundlich isotherme.

Several methods of utilizing the relation (1) in order to determine the K constant and the number m have been employed.

1. The K constant is equal to the inverse of the concentration (A) when r/m to equal to the value 1/2, that is to say when the large molecule G is half saturated.

2. One can, in the manner of Klotz[35] express the experimental values of 1/r as a function of experimental values of 1/A which can yield an expression:

$$\frac{1}{r} = \frac{1}{m} + \frac{1}{mK(A)} \qquad (4)$$

The slope of which is equal to 1/mK and which intercepts the ordinate axis at the value of 1/m.

3. One can obtain an expression if one expresses r/(A) as a function of r:

$$\frac{r}{(A)} = mK - rK \qquad (5)$$

The ordinate is intercepted by a value equal to mK and the abcisse by a value equal to m. That procedure utilized by Scatchard[52], puts some important evidence in the implicated extrapolation in the determination of constants. Evidently the (1) relation corresponds to limited conditions, the independence of local diverse reactions among molecules A and G groups are only feasible if these groups are sufficiently isolated one from another. Of those things that concern the immunological combinations, Morales, Botts and Hill[41] have examined, from a theoretical point of view, ~~in~~ the case of other complexes, where the antibody molecules on the antigenic surface are mutually attracted or repelled. They have also outlined the calculation of the influence exercised on the equilibrium by the progressive changes of the effects of translation of rotation, to thecourse of growth of the aggregate.

B. Study of isohemagglutination

1. Reversibility of isohemagglutination.

The cellular combinations are not being presented from the point of view which ~~we hold~~ IS HELD that the only viewpoint from which the antibody can be considered is practically univalent. There are ~~offered~~ methods of techniques ~~of making~~ FOR SEPARATING the total complexes ~~seperate~~ by centrifugation, the antibody ~~remaining~~ WHICH REMAINS free can be determined in the liquid supernatant.

However, the preliminary results obtained have not led to results easy to interpret.

The most clear cut are those of Eisenberg and Volek[9] on the absorption of agglutinin by the typhoid bacillus and of Cromwell[7] on the absorption of hemolysin by the red cell. If one plots on the abcissa the log of free antibody and on the ordinate the quantity of antibody combined, one obtains on occasion straight lines, that is to say, that the relation is of the Freundlich isotherm type. It is necessary to see, after that which has been said previously, the consequence of the heterogeneity of antigen.

~~One knows~~ It is known, qualitatively, from Landsteiner[37] that the agglutinated red cells (by normal human sera) release much agglutinin by heating to 50-60°. ~~One~~ We can ~~thus~~ therefore hope that the process of isohemagglutination shows itself favorably for a quantitative study. Effectively in the course of a series of researches on the serum of individuals of blood group A and O put in the presence of cells of Group B, and on some serums of individuals of group B put in the presence of cells of group A, it has been possible to demonstrate the reversibility of isohemagglutination and to measure the enthalpy and the free energy of the combination of agglutinins with the agglutinogic group. The reversibility of the total process, that is to say, the secondary action, agglomeration of cells, as well as the primary action, fixation of agglutinin, has been established by Filitti-Wurmser and Jacquot-Armand[10], in the manner of two types of ~~experiences~~ experiments, displacement of equilibrium by temperature and by variation of volume.

1. If at ~~the~~ a time ~~to~~ when a given volume of serum from an individual of blood group A one adds an increasing number of red blood cells from an individual of group B, ~~agglutination increases~~ ~~one sees~~ we find that the number of red cells agglutinated increases up until a maximum value. This value is increased when the temperature is lowered. For certain serums, the effect is considerable, we shall see later that these are those coming from individuals whose blood genotype is A_1O. This ~~strand~~ striking exothermicity has been put to use in order to gain evidence of the reversibility of the action of temperature.

The rate of agglutination related to the number of red cells agglutinated AND to the number of red cells present has been measured by a certain mixture of red cells and serum, one part at 37° and the other part at 5°C. The results have been compared with the rate of agglutination of a mixture prepared in identical manner but which having FIRST BEEN submitted ~~first~~ to agglutination at 5°C and WHICH was then carried to 37°C. These results are presented in Table I.

These results demonstrate the reversible equilibration with temperature. ~~One has~~ WE HAVE studied moreover the agglutination obtained by elution at 37°C, with an agglutinate formed at that same temperature. This agglutinin put in the presence of B red cells acts according to temperature as the serum from which it comes. ~~Then there is nothing else in a serum of~~ THEREFORE, WE DO NOT HAVE TO DEAL WITH TEMPERATURE IN SERUM CONTAINING apparent several anti B agglutinins capable of acting at different temperatures, but ~~certainly~~ ONLY WITH a ~~simple~~ SINGLE ~~isoagglutinin~~. AGGLUTININ.

2. The rate of agglutination at 37°C for a given quantity of red blood cells and of serum in a given volume V has been compared to the rate of agglutination which is obtained following an inverse course.

~~One operates~~ WE PREPARE the agglutination ~~feat~~ FIRST of all with the same quantity of red cells and serum in a smaller volume than v and following this one effects the convenient dilution in order to obtain the V volume.

Table II summarizes these experiments of reversibility by effective dilution on several serums. The reversibility of isohemagglutinates has been recently confirmed by Wilkie and Becker[58].

Table I

RATE OF AGGLUTINATION OF A MIXTURE SERUM $A_1\beta$ + SUSPENSION OF RED BLOOD B AT 37°, AT 5° AND AT 5° AFTER AGGLUTINATION PREVIOUSLY AT 5°C.

At 37°	At 5°	At 37° After Agglutination at 5°
0,18	0,55	0,20
0,19	0,64	0,17
0,69	0,83	0,72
0,97	0,99	0,98

I. Rate of agglutination of the mixture of serum (A_1O + suspension of red blood cells H) in volume v.

II. Rate of agglutination of the mixture in vol. V.

III. v/V

IV. Rate of agglutination after dilution

I	II	III	IV
0,95	0,57	1:5	0,57
0,86	0,60	1:5	0,54
0,96	0,88	1:8	0,83
0,96	0,87	1:8	0,86
0,93	0,89	1:8	0,89
0,85	0,65	1:8	0,67
0,83	0,57	1:8	0,62
0,81	0,51	1:8	0,56
0,82	0,71	1:8	0,73
0,78	0,33	1:8	0,34
0,90	0,76	1:10	0,77
0,86	0,65	1:10	0,64

2. Application of the Law of Mass Action

Let us now envision the primary act of isohemagglutination.

In a series of researches, Filitti-Wurmser, Jacquot-Armand and Wurmser have applied to this the laws of chemical equilibrium. Let K be the intrinsic constant of combination of an agglutinogin group G with a molecule of agglutinin A. Let m be the number of G groups accessible on a red blood cell and h the molar concentration of the red blood cells. As the G groups are without interaction, one has after equation 4, calling A and A_f the concentrations of agglutinin liberated and agglutinin fixed:

$$\frac{h}{(A)_f} = \frac{1}{m} + \frac{1}{mK(A)} \qquad (6)$$

The slope of the straight line which represents the values of $h/(A)_f$ as a function of $1/(A)$ is inversely proportional to mK and, since m is a constant, the

the relation of the slopes at two-temperatures permit the calculation of the ~~calculation of the~~ changing enthalpy. ΔH corresponding to the combination of a molecule of agglutinin with an agglutinogin group (59).

It suffices in order to obtain ΔH to be able to express the agglutinin in relative values. One can determine with precision the relative concentration of isoagglutinin ~~after~~ By the maximum number of red blood cells which can be agglutinated under well defined conditions. This has been established by progressively diluting the same sera and measuring the maximum number of red cells agglutinated by a mm^3 at 4°C in a mixture consisting of 0.6 cm^3 of serum plus or minus diluent and 0.3 cm^3 of a suspension of red cells. Let us call N_4 the number thus found and φ the relation of N_4 to the molar concentration of agglutinin. When a mixture of sera and red blood cells obtains its equilibrium at a certain temperature, the agglutinin remains free and is measured after centrifugation by the maximum number N'_4 of red blood cells which the liquid supernatant can agglutinate at 4°C in the indicated condition for the determination of N_4. As to the fixed agglutinin, it is obtained by the difference between the number N_4 and N_4'. Allow N_f to be that difference and N_t the total number of red blood cells present, the ~~relation~~ RELATION is

$$\frac{N_t}{N_f} = \frac{6 \times 10^{17}}{m\varphi} + \frac{6 \times 10^{17}}{mKN'_4} \qquad (7)$$

The variation of enthalpy ΔH is obtained from determining ~~same~~ values at two temperatures of N_t/N_f and N'_4, which result uniquely from the numbers of red blood cells. These numbers are determined ~~either~~ by ~~hemocytometer~~ HEMOCYTOMETER EITHER BY BEING read directly by microscope or ~~by~~ BEING PUT ON microfilm.

3. Classification of ANTI-B isohemagglutinins ~~anti-B~~

For the sake of clarity of that which follows, we will say a few words on human isohemagglutination. There exists normally to the sera of individuals of blood groups B or O two anti-A agglutinins ~~anti-A~~, one α acts at the same time on blood

cells A_1 and A_2, the other α acting only on the red cells A_1. The serum of individuals of blood group A and O contain an anti-B isoagglutinin ~~anti-B~~. One of the results of the thermodynamic study of isohemagglutinates[11] has been to make known (1) that there exists diverse anti-B isohemagglutinin; (2) there is in a given serum A or O only one of these isoagglutinins. The multiplicity of isohemagglutinin anti-B is apparent as a consequence of the study of 26 serums derived from individuals of blood group A. After having eliminated complement, the study of the influence of temperature on agglutination of blood cells had led to the division of these serums into a small number of classes. It has been found that ~~if one was~~ they were confined to the same class if one divided the serums according to their origin from individuals of subgroups A_1, A_2, A_3. Moreover among the 22 serums of subgroup A_1, since two were different from the other 20, ~~one~~ we could show that they act in fact like sera from individuals of genotype A_1A_1.

All these anti-B isohemagglutinins have then been designated by symbols relating to their original genotype $\beta(A_1O)$ $\beta(A_1A)$ $\beta(A_2)$ $\beta(A_3)$. And the anti-B isohemagglutinin present in the serum of the individuals of group O has been called $\beta(OO)$ because it also has its own characteristic properties[12].

4. Measurement of enthalpy.

Figure 1 demonstrates the experimental results obtained with serum A_1O, A_1A_1 and O at 37°C. The values of $1/N'_4$ are on the abcissa and the value of N_t/N_f are on the ordinate. One sees that the linear relation is well verified. The representative lines cutting the axis of the ordinate at the neighborhood of the origin is a consequence of the magnitude of the number of m groups (agglutinogene) present on a red cell. The slope of each line then is practically equal to $(N_t/N_f)N'_4$. Table III establishes, this from ~~that~~ the work already cited[11,12,14] and that of Mavrides[40] which utilizes ~~indicates~~ the slopes of the line calculated by the method of least squares and the values of ΔH which are deduced from them, expressed as Kcal per mole of fixed agglutinin.

TABLE III

Isoagglutinin (ref.)	Agglutinogen	Slope X 10^{-5} 37°C.	Slope X 10^{-5} 25°C.	$-\Delta H$, Kcal
$\beta(A_1O)$ 11	B	1.51 ± 0.07	0.54 ± 0.06	16 ± 2
$\beta(A_1A_1)$ 14	B	2.34 ± 0.08	1.53 ± 0.07	6.5 ± 1.1
$\beta(A_2)$ 11	B	0.43 ± 0.07	0.24 ± 0.04	9
$\beta(OO)$ 12	B	4.00 ± 0.14	3.69 ± 0.04	1.7 ± 0.4
$\alpha(BO)$ 40	A_1	2.47 ± 0.25	0.71 ± 0.07	19 ± 3
$\alpha_1(BO)$ 40	A_1	100 ± 13	12.1 ± 0.64	33 ± 2.5
$\alpha(BO)$ 40	A_2	-	3.28 ± 0.64	-

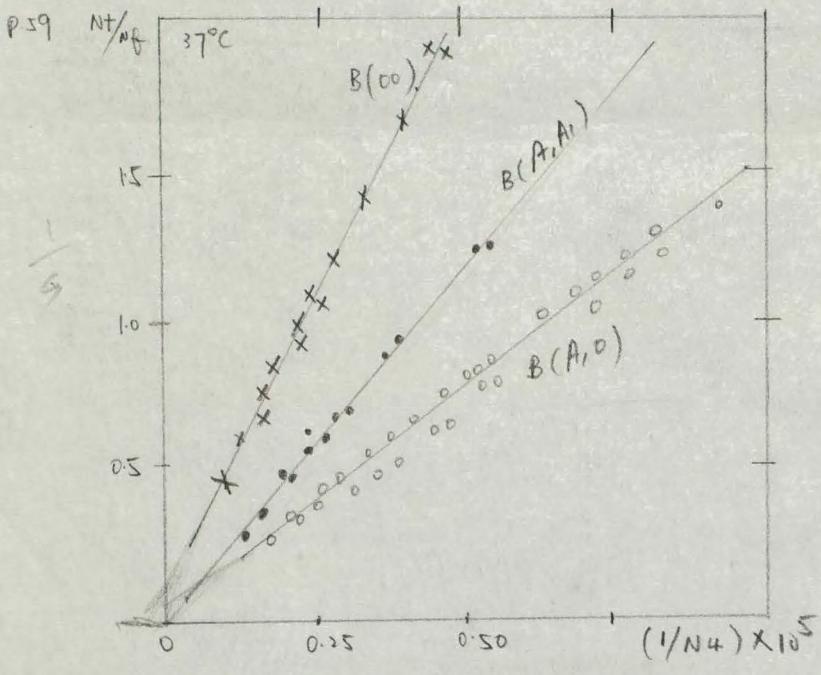

Fig. 1. Inverse of fixed agglutinin on a red cell as a function of the inverse of free agglutinin (in relative values for 3 types of agglutinin.

5. Determination of equilibrium constants

Up until now the concentration of combined agglutinin and free have only been expressed by their relative values N_f and N'_4. But if we wish to obtain K from relation[7] it is necessary to know the coefficient of equivalence between the relative concentration of isoagglutinin expressed by numbers N_4, N_f and N'_4 and the molarities that they represent. The coefficient a once known, WILL ENABLE the number n of agglutinogen groups present on a red cell ~~will be able~~ to be measured experimentally.

The calculation of a is based for each type of agglutinin on two determinations, those of molecular weight of agglutinin and those of N which can be combined specifically in a serum in which N_4 is known.

1. Molecular weights. The molecular weights of 3 isoagglutinins anti-B, $\beta(A_1\phi)$, $\beta(A_1A_1)$ and $\beta(OO)$ have been evaluated by measuring sedimentation constants[13]. These measurements have been effected with a Spinco ultracentrifuge, by the analytical method of Tiselius, Pedersen and Svedberg[57]. The relative concentrations of agglutinin from one part and from the other PART of the partition separating the central and peripheral compartments was determined by the maximum number of red cells agglutinable at 4°C. The values of sedimentative constants extrapolated to infinite dilution and at 20°C, S_{20} are respectively 15.5×10^{-13} for $\beta(A_1O)$, 11×10^{-13} for $\beta(A_1A_1)$, 6.5×10^{-13} for $\beta(OO)$. In making the customary hypothesis, one finds that the probable molecular weight of these three isoagglutinins are respectively: 500,000 for $\beta(A_1O)$, 300,000 for $\beta(A_1A_1)$ and 170,000 for $\beta(OO)$.

2. Coefficient of equivalence. The coefficients of equivalence have been determined by combination of agglutinins with ~~some~~ stromata of B red blood cells and the microdosage of nitrogen thus fixed[12,31].

Finally, to eliminate the amount of nitrogen arising from nonspecific protein, a quantity of B stroma equal to that put in presence of serum Anti-B

was agitated with some A_1B serum. Moreover some measurements effected with anti-B serum different only by their relative concentration of agglutinin (N_4). The values of α obtained are respectively 1.7×10^{14} for $B(A_1O)$, 1×10^{14} for $\beta(A_1A_1)$, 0.6×10^{14} for $\beta(OO)$. Knowing α, it is possible to determine m by dividing the number of fixed agglutinin molecules in the region of saturation by the number of red cells present. A value of $\neq 5 \times 10^5$ has been obtained for m with BO and A_1B red cells.

Table IV recapitulates these diverse facts and those which arise from them, intrinsic constants in liter/mole, variations of standard free energy in Kcal per mole of agglutinin, and variations of entropy corresponding to calorie/degree.

TABLE IV

	$\beta(A_1O)$	$B(A_1A_1)$	$\beta(OO)$
$\alpha = N_4$/molarite	1.7×10^{14}	1×10^{14}	0.6×10^{14}
K (37°), litre/mole	8×10^6	5×10^6	3×10^6
K (25°), litre/mole	22×10^6	8×10^6	3.3×10^6
K (4°), litre/mole	170×10^6	22×10^6	4.2×10^6
ΔF (25°), Kcal	-10	-9.4	-8.9
ΔS (25°), cal/deg	-21	+9.7	+24

6. Interpretation of results

The results of a thermodynamic study of isohemagglutination may be envisioned from two points of view, that which may be learned about the structure of isoagglutinin and that which can be learned about their formations.

1. Information on structure. This information is limited by the fact that the obtained data on the heat of reaction and entropy are evidently round figures which depend on all the known processes in the combination of agglutinin:

local reactions among the specific groups and disturbances produced in the rest of the molecule. The enormous influences between the variation of entropy which accompany the reactions of agglutinin $\beta(A_1O)$, $\beta(A_1A_1)$ and $\beta(OO)$: -21, +9.7, +24 allow little doubt that these disturbances are important. The groups of atoms which are implicated in the union of agglutinin with agglutinogen B may be very similar to the diverse anti-B agglutinin since they are precisely responsible for the opposing specificity of agglutinogen B. There is then room for attributing the observed differences to that which takes place in the region of specific groups. It may act by displacing some more or less important molecules of H_2O in accordance with the dimension of the surfaces in contact. But the increase in entropy can also correspond to some intramolecular change of the agglutinin. These reversible changes would ~~draw together~~ RESEMBLE those changes which are produced when certain enzymes, such as urease and pepsin form a complex with their substrate.

Another remark has been made in the course of a study on the influence of temperature on agglutination[60]. It concerns the valence of isoagglutinins.

One can prove that the mean number of molecules which are able to be fixed on a red cell of the former, (A,O) that are agglutinable varies with the temperature more than those from the combination of that agglutinin with the agglutinogen which is more exothermic. For example, for the same rate of agglutination, 0.5 obtained with serum A_1O (ΔH = -16 Kcal), one finds that the number of molecules of fixed agglutinin present on the red cell is 1600 at 4°C and 4000 at 37°C. For the same rate 0.5 obtained with serum O (ΔH = -1,7 Kcal) this number is 10,800 at 4°C and 13500 at 37°C.

The most simple ~~explation~~ EXPLANATION is that the red blood cells attach themselves one after another by the second group of a molecule of agglutinin of which the first group is already combined. This bivalence does not intervene in the calculation of equilibrium because for geometric reasons, a small portion of agglutinin molecules can be fixed at the same time on two red blood cells. But the adhesion

of red blood cells does not remain unless a reaction is started putting in motion the same assemblage of atoms as the fixation of independent agglutinins, and the effect of temperature on affinity may be of the same order as the two processes.

2. Formation of isohemagglutinins. The facts established in the preceding paragraphs have raised several questions concerning the formation of isoagglutinins.

In the first place, there are the measurements of enthalpy and free energy of combination of B agglutinogen with isohemagglutinin anti-B which has to do with the discovery of the plurality of the former. The same measurements have demonstrated that the serum of a given individual contains only one type of anti-B isoagglutinin. That homogeneity is caused by the manner by which the law of mass action can be applied to the agglutinin produced by a serum, without actually fractionating, for the linear relationship was verified with an approximation of 5%. There is a characteristic which distinguishes the isohemagglutinin from immune antibody. It is intimately related to the existence of a genetic mechanism present in the formation of isohemagglutinins. On this subject, the differences are so marked ~~that one observes~~ between the agglutinin $\beta(A_1O)$, $\beta(A_1A_1)$ and $\beta(OO)$ ~~that they~~ to be are particularly suggestive. It proves that there is no heterozygote dominance of the genes but a cooperation of the two alleles in the production of a hybrid molecule $\beta(A_1O)$.

A confirmation of this fact proceeds ~~still~~ further from the study of mixture of anti-B isohemagglutinin[15]. One should have been able to think that the properties of serum A_1O resulting from the presence of a combination are very ~~little dissociable from~~ similar the two agglutinins $\beta(A_1A_1)$ and $\beta(OO)$. Experience has shown that ~~there~~ THIS is none TRUE. One has calculated the relation N_s/N_f as a function of $1/H'_4$ for mixture of serum A_1A_1 and O, in admitting that the two agglutinins are combined with the agglutinogene group conforming to the equilibrium constant which

which are there and which are indicated in Table IV. One has found that the experimental points fall well on the calculated curve. In the region where the former is almost linear, the slope is, for example, at 37° about 3×10^5; it is intermediate between the slopes which correspond to isoagglutinins $\beta(A_1A_1)$ and and $\beta(OO)$ when they are alone, and which are respectively 2.3×10^5 and 4.0×10^5. The $\beta(A_1O)$ agglutinin which gives a slope of 1.5×10^5 can hardly be confused with a mixture of $\beta(A_1A_1)$ and $\beta(OO)$.

In summary, each agglutinin in order to be fixed on the agglutinogen in competition with another, conforms to the law of mass action and without interaction. On the other hand, one observes that in these mixtures, the product $(N_1/N_2)\ N'_4$, conforming to the calculation, varies with the total concentration of agglutinin present, contrasted with the results obtained on individual serums ~~xxx~~ in which the homogeneity is thus confirmed.

The existence of a hybrid molecule $\beta(A_1O)$ revealed by the thermodynamic study of agglutination, confirmed by the measurements of speed of sedimentation, poses the problem of the collaboration of two alleles in the synthesis of a protein. That question has been discussed elsewhere[60].

There is yet another question which concerns this time the agglutinogen. The measurements related to this have been put in evidence of the nature of the identity of B agglutinogen groups present on the red cells BO and A_1B. Certainly, their number is the same on a red cell within the limits of the precision of measurement since these groups are found under the influence ofgenes A, B and O and some points are predestined on the red cell.[12].

III. Combinations of Haptens with Antibodies

A. Determination of a mean intrinsic constant

The study of equilibrium between haptene and antibody does not differ in principle from the usual study of reversible combinations of proteins with small

molecules. But a complication is introduced by the fact of heterogeneity of antisera, that is to say, the simultaneous presence of antibody of unequal affinity for haptene.

Pauling, Pressman and Grossberg[19] have admitted in a theory of competition between haptene and antigen, which will be questioned a little later, that the heterogeneity of antibody can be described an an error function in the free energy of combination of haptene with antibody. Let K represent the constant of inhibition, that is to say the equilibrium constant of a haptene with a particular antibody, K_0 a mean constant and the index of heterogeneity. The fraction of antibody molecules for which $\ln (K/K_0)$ is included between K/K_0 and $\ln K/K_0 + d \ln (K/K_0)$ a value:

$$\frac{1}{\sqrt{\pi}\sigma} \exp \left\{ - (\ln (K/K_0)^2 / \sigma \right\} d(\ln (K/K_0))$$

The same hypothesis has been adopted by Eisen and Karush[8] when these authors wished to apply relation[1] to the combination of an antibody with univalent haptene. The problem has been treated in a general manner in another case[33]. But one can utilise simply the fact that no matter what value of σ be, the relation r/n is equal to 1/2 when the inverse of haptene concentrate 1/(H) is equal to the mean intrinsic constant K_0.

Eisen and Karush have immunized rabbits with sheep serum coupled with diazotized arsenilic acid. The antibody was fixed on stromata of human red blood cells coupled with the same component. They immediately eluted by taking the pH to 3.8. The coloring homologous haptene was p(p-OH phenyl azo) phenyl arsonic acid. The antibody solution of known concentration was placed in a cellophane sac and equilibrated with a colored solution in which the initial concentration was equally known. By spectrophotometry ~~are~~ was determined the concentration (H) of the color remaining free, which allowed the calculation by difference of the number r. Figure 2 represents the obtained results in plotting 1/r against 1/(H). The extrapolation to the ordinate gives the value 2 for n, or another way of saying

the antibody is bivalent. The value of K_o then corresponds to the value of 1/(H) when 1/r is equal to 1. One finds therefore that K_o at 29°C is equal to 3.5×10^5 liter/mole which assigns the variation of mean free energy the value of 7.7 Kcal per mole of haptene. Some analagous dialysis work, done by Lerman[38] who has put on the haptene ~~preferred~~ PREPARED by coupling diazotized arsanilic acid 8 amino 1-naphthol-3,69disulfonic acid. The antibody was highly purified. The free energy of combination at 39°C has been found equal to -6.8 Kcal per mole of haptene.

Fig. 2. Moles of antibody per mole of haptene plotted as a function of the inverse of the concentration of free haptene.

B. Study of forces ~~intervening~~ ACTING in the union of haptene with antibody.

When a molecule bears only a single haptenique group it can certainly combine with antibody but cannot form a precipitate. Its combination can however be made evident thanks to the phenomenon of inhibition discovered by Landsteiner[36]. This phenomenon consists of ^ OBSERVING the diminution of the precipitate formed in presence of antiserum and antigen. Pauling, Pressman, Campbell and Ikeda[48] have developed a theory of competition between haptene and antigen based on a common chemical equilibrium. A bivalent antigen G, a bivalent homogenous antibody A, and a univalent haptene H give complexes made up entirely by GAG, HA, HAG and HAH, and a precipitate GA of definite solubility. In the zone of equivalence, where the total molar quantity of G and A are equal, the quantity of precipitate may

be in a linear relation with the quantity of haptene present. The corresponding slope may be proportional to the constant of inhibition. That relation is only verified at very weak concentrations. Taking into consideration then, the heterogeneity of antisera, one admits as we have seen more often, that the discrepancy between a mean value and the diverse free energy of combinations with haptene follow a Gaussian curve. The relation of the quantity of precipitate in presence of haptene to the quantity of precipitate in absence of haptene can be calculated as a function of K_0, of the mean value of the constant of inhibition, of σ the index of heterogeneity, and from the total quantity of haptene.

The shape of the curve obtained inverse in plotting the quantity of precipitate against the logarithm of the total quantity of haptene serves first of all to determine σ. As to the changes in the value of K_0, they have an effect of displacing the curve along the length of the axis of the absicca.

Certain of departing hypotheses, relative to the reaction between antigen and antibody are in contradiction with the ideas which will be introduced in Chapter IV. For example, even as Hershey[30] has observed, the solubility of specific precipitates is generally comprehended to be the sum of the component concentrations of small fractions. But it suffices, in order to draw the conclusions which are of general interest that the relation representing the inhibition experiments certainly have the significance given to them. It thus permits the comparison of K_0 values corresponding to diverse haptenes and the calculation of differences of free energy. One can, in summary[47] consider precipitation with antigen as a method for fixing a concentration of standard free antibody.

In the ensuing measurements for two haptenes, the quantities at which reduce the concentration of antibody to that standard value, one obtains finally relative values of constants of inhibition of two haptenes. That method has made possible a new category of research. It has been demonstrated that the constants of

inhibition depend strictly on the degree of similarity of four of the haptenes with the immunizing haptenic group, as if the antibody reproduced an exact template of the form of the haptenic group within a precision of 1A°. The comparison of constants, for a series of related haptenes, containing convenient substituted groups, permits the recognition of the diverse intermolecular forces which are thrown into play: Forces of electronic dispersion and attraction of London due to the electric charges of opposite sign in the haptene and antibody. A typical example[51] is the comparison between two haptenes one of which contains the phenyl trimethyl ammonium group charged positively, and the other, the butyl tertiary benzene group non-charged. The ratio of inhibition constants at 5°C is 15.5, by consequence the difference between the free energies is 1.5 Kcal/mole. If there is an electrostatic potential energy, it corresponds to two charges separated in the water by 7A°. But the radius of the positive and the probable position of the negative charge situated in the antibody are such that it can be trusted up to a minimum of 4.9A°. From all evidence the Coulomb forces certainly play the role one has ascribed to them. Moreover, one finds there a supplementary proof that the forces of specific attraction between antibody and antigen depend very strictly on the degree of resemblance of their molecules.

IV. Specific Precipitation

A. General Characteristics of Specific Precipitation

One of the features which distinguishes the point of view of the thermodynamic application of specific precipitation from the immunologic reactions studied previously, is a large difficulty in demonstrating complete reversibility.

Certain antigen-antibody complexes can be dissociated but only in the presence of strong saline solution. That is the case of the carbohydrate anti-carbohydrate studies by Heidelberger's school[26,27]. For anti-protein precipitates, the dissociability has only been described for the ovalbumin anti-ovalbumin system and still to a weak degree, in a work by Oudin and Grabor[42]. From the work of Heidelberger and Kendall[23-25] the composition of the washed precipitates of ovalbumin anti-ovalbumin

are not perceptibly affected by the volume in which the precipitation was produced. The precipitate seemed to depend only on the total quantity of antigen and antibody present. In contrast, a property of a specific precipitate, is their solubility in an excess of antigen, and at times in an excess of antibody. This may be most easily interpreted by reversibility of the reaction. Several theories have been proposed in order to give value to the absence of volume effect without completely abandoning in every case the concept of reversibility. These theories differ mainly in the conception of the mechanism of insolubilization. It is known that there are on this point two points of view, already described with regard to agglutination. According to Bordet's conception(2), the surface of the antigen molecule in covering itself with antibody molecules becomes sensitive to the flocculating action of electrolytes. Moreover, Marrack(39) has made the suggestion that the apposition of polar groups of antibody on those of antigen may tend to diminish the attraction of water and that effect, in agreement of Boyd(3) can also result in a steric hindrance. According to Marrack(39) Heidelberger(20) and Pauling(46) the essential fact of precipitation is the putting in motion of specific forces: the antigen and antibody being multivalent toward one another, making up sort of a lattice which grows up until the time the particles become large enough to separate out from the solution.

Since there is no doubt of the multivalency of antigen, we see that the problem therefore rests with that of antibody. Strong presumptions are in favor of its bivalence. But one cannot exclude without reservation the contrary opinion, in which certain antibodies are univalent and others bivalent as Herowitz believed(18). We will consider then the two possibilities.

First let us recall that most of the experimental facts rest on the following type of experience. A series of tubes contains the same quantity of anti-serum. One then adds increasing quantities of antigen of which the amount of nitrogen is known, and consequently the number G_0 of corresponding antigen molecules. For each tube the nitrogen precipitated is determined. If one plots the result as a function of antigen added, we observe a maximum. By sensitive tests, it is possible to determine precisely

which are the tubes where the liquid supernatant gives no more reaction with antibody or antigen. This is designated the equivalence zone. The amount of N (total) of the precipitate in the tubes of that zone permits the determination, by difference with the antigen N, the N of the precipitate antibody. The quantity thus found is a measure approaching the antibody N present in all the tubes. It is a minimum, because there can be soluble complexes. Moreover, if the combination of G with A is reversible, there always remains free antibody. Finally, in order to pass from the quantity of N to the number of moles of antibody A_0 a new approximation is introduced, from the fact of heterogeneity, since one does not know exactly the mean molecular weight to the number of molecules.

B. Theories Based on Univalence of Antibody

The relation(1) is established for a univalent antibody. We have indicated at times some isoagglutinins which can ~~only~~ be applied to the combination of antigen with bivalent antibody ~~when~~ ONLY IF the proportion of antibody molecules is 1/2 that of LINKED to two molecules of antigen. The ~~isohemagglutin~~ RELATION is ~~lacking in this respect.~~ UNIMPORTANT for that reason.

That relation, which is equivalent to that of Ghosh(16) represents well, for example, the neutralisation of tetanus toxin by antitoxin. In the zones of aggregation the(1) relation is valid only for a univalent antibody. It then fixes a mean value of the quantity of combined antibody for a given quantity of free antibody. There exists in fact a statistical division composed of GA, GA_2 GA_n....GA_m. For increasing values of (A), there is a predominance more and more marked of complexes corresponding to high values of N. Admitting with Teorell(56) that the precipitates are due to the insolubility of the total or of certain single components of these complexes, and it is important that the precipitation does not exclude those from participating in the equilibrium. On the other hand, in place of that, the successive constants K_1 K_2 K_n differ only by their statistical term, which is the basis of relation(1), let us consider that they have any value whatsoever. Theorell shows that if these values are conveniently chosen, one obtains, as a function of the quantity of antigen

added to antiserum or inversely, a distribution of complexes which is consistent with the known facts: the variable composition of the precipitate, solubility of precipitate most rich in antigen (antigen excess) (case of rabbit antisera) or solubility not only of these precipitates but also of those which are rich in excess antibody (horse antisera), finally the minimum effect produced by dilution.

There have not been attempts of quantitative application from the theory of these particular cases, but one can reconcile the research where antigen antibody precipitates are considered as corresponding to a formula GA_n because the equilibrium constants can be such that the precipitate may be formed practically from a lone complex.

Two antiazoprotein systems have been studied by Haurowitz, Crampton and Sowinski[19]. These authors have measured, after washing, the solubility in saline suspension of specific precipitates obtained with tagged antigen and the homologous antibody of the rabbit. They admit that the solution contains essentially the antibody arising from the dissociation:

$$GA_n \rightleftharpoons GA_{n-1} + A$$

One can then calculate an equilibrium constant. The experiments have been done at two temperatures, which furnishes an evaluation of enthalpy. The results are the following, ΔF and H were expressed in Kcal/mole S in cal/mole degree, and all this data corresponds to the formation of complexes.

Antigen	$-\Delta F$				$-\Delta H$	ΔS
Arsanilic-bovine serum globulin	5°C	8.0	25°C	8.4	2.0	21
	5°C	8.0	25°C	9.3	2.1	21
	4°C	8.5	29°C	9.0	2.7	21
Sulphanilous ovalbumin	4°C	8.7	29°C	9.2	3.0	21

Thus Campbelland Bulman[6] remark that it is necessary to be assured that the supposed dissociation equation certainly represents the processes studied. New experiments by Haurowitz confirm his first results (personal communication). In washing the precipitate one never carries anything but antibody. But the results of analysis show that N, is comprised between 5.6 and 6.7, which indicates the existence in the precipitate of a mixture of GA_6 with GA_5 or GA_7. Moreover, if one repeats the

the washing of the precipitate with a solution of NaCl 0.9 p. 100, one observes an increase in the experimental value for ΔF.

C. Theories based on the lattice hypothesis.

In that conception, the precipitate consists of aggregates in three dimensions, more or less large, of which the skeleton is formed by some multivalent molecules of antibody laying between those of antigen molecules. The latter carry a more variable number of antibody molecules of which a single group has reacted. What is the proportion of antibody molecules incompletely saturated to the ratio of the saturated molecules? To be able to answer that a theory is required susceptible to proving the composition of the precipitate and measuring the affinity of the antibody for antigen.

Hershey(29) in one of his interesting publications on this subject, has wished to avoid the difficulty by imagining that the antibody behaves during an initial phase as if it were univalent, the bivalence only comes into play in aggregation. By use of probability applied to the kinetics of that second phase, he confines it to a relation between the composition of the precipitate and that of the initial mixture in equilibrium for which the relation(3) was valid. Hershey(28) found for the intrinsic constants of the antiovalbumin system of the rabbit a value of 2.9×10^5 liter/mole. But we cannot retain the idea of a period during which a molecule of antibody in spite of its bivalence is never associated with a molecule of antigen.

A partial treament of the problem is due to Kendall(34). It uniquely concerns the zone of excess antibody where the well known relation of Heidelberger and Kendall is verified. This can be put in the form.

$$\text{Appt} = M G_0 - \frac{M^2 C_0^2}{H A_0} \qquad (8)$$

A_0 and G_0 are respectively the number of molecules of bivalent antibody and of multivalent antigen present in the system. Appt is the number of molecules of antibody in the precipitate. It means that the composition of the precipitate and

its quantity are determined by the functional properties of the reagents and their properties in the initial mixture. In order to obtain that relation by a single use of probability, Kendall, out of the usual hypothesis of equal reactivity of all the group, admits two other conditions: 1) all molecules of antibody which have reacted, by one of its two groups is in the precipitate. 2) The degree of the completeness of the reaction has attained its maximum value.

Goldberg (17) has recently given a more general theory in which the equations (1) and (8) constitute a particular used and which has already permitted a determination of equilibrium constant. It consists of describing the most probable distribution of portions and of the composition of aggregates constituting the precipitate. The statistical method is that of Flory, extended by Stockmayer, and which has been used by these authors for the study of branched polymers. The hypotheses are based on the following: the precipitates are formed by aggregation in three dimensions from united multivalent GA. There do not have to be any reactions carrying out a cyclic structure, which determines the numbers of links in an aggregate of given size. As in the other theories all the energy of combination between two reactive groups are supposed equal, whatever may be the size or form of the aggregate which these bonds reunite. In order to calculate the most probable distribution, Goldberg considers the reaction proceeding reversibly by combination of an increasing number of group G of the antigen G with A groups of the antibody A. The system acts by a series of the most probable states, that is to say, maximum entropy. The distribution can then be calculated for a certain degree of advancement of the reaction p_2 defined as the ratio $(GA)/((G) + (GA))$. Goldberg has treated the case of a mixture of bivalent antibody and of multivalent antigen which can also hold for some univalent antibody. This mixture is constituted by aggregates of which each type is characterized by the number i, j, k of these three substances. If one knows the approximate composition of the system and the degree of advancement of the reaction, one has the means to determine the number of each type of aggregate even as is done for molecules of antibody and free antigen.

Let there be a system composed of G_o molecules of antigen, A_o molecules of bivalent antibody, D_o molecules of univalent antibody. Let us call r the ratio ~~xm~~ $mG_o/2A$ of the number of antigenic groups to the number of bivalent antibody groups, q the number of free antibody on an aggregate and p the proportion of groups of antibody belohging to bivalent molecules. The number of aggregates having the composition i, j, k is:

$$N_{ijk} = mG_o \frac{(mk - k)!}{(mk - 2k + 2 - q - j)!k!q!j!} 4^{k-1} p^{k+i-1} \times$$
$$p^{k+i+j-1} (1 - p)^{mk-k-i-j+1} (1 - ppr)^{i-k+1} (1 - p)^{j} \qquad (9)$$
$$i = k - 1 + q; \quad 0 \leq q + j \leq mk - 2k + 2$$

The theory predicts the essential facts of specific precipitation. There exists a certain degree of progress of the reaction for which the system passes abruptly from a state characterized by many small aggregates to a state characterized by a small number of enormous aggregates. This critical degree of advancement and the composition of the precipitate at this point depends only on the valence of the antigen and relation of the quantities of reagents put together. The degree of maximum advancement of the reaction and the corresponding composition of the precipitate depend also only on the functional relation. We are then within reach of calculating for these two degrees of advancement the mean values of the number of antibody molecules in an aggregate containing a given number of antigen molecules and, from that the mean relation of the antibody to antigen in all the aggregates containing more than one molecule of antigen. The calculation has been made by admitting that there arenot univalent antibodies, and the results have been compared with the molecular relationship of antibody and antigen in the precipitates studied by Heidelberger and Kendall[25], Kabat and Heidelberger[32] and Pappenheimer[43]. One had to wait until the observed relationships were included with the calculated relationships for the critical degrees of advancement and maximum, since they correspond to the beginning and to the maximum of precipitation. The agreement has been

very satisfactory.

The theory assigns limits to the anti body antigen relation for which the critical zone can be attained. It gives understanding to the existence of zones of inhibition, imposed by the functional relationship but evidently depending also on the solubility of aggregates.

In approaching the regions of excess antigen and excess antibody the aggregate becomes more and more small and finally becomes soluble.

It is then possible, in having recourse to a technique of electrophoresis or of ultracentrifugation to appreciate the concentration of free antigen. Stemming from that portion, Goldberg's distribution makes known the concentration of the other aggregates. Singer and Campbell[54] have studied in that manner the equilibrium between serum slightly ovalbumin iodinate and the antibody of the rabbit prepared with non-iodinated protein. The proof had been done previously by ultracentrifugation and electrophoresis[53] that the antibody is largely bivalent. If the general relation[9] is used which is simplified in this case, the expression of the concentration of free antigen (G) and of complexes (GA) and (G_2A) is a function of the degree of advancement of the reaction p. Thus one has for (G) the expression $(G)_o\ (1 - p)^m$. It permits obtaining p from the value of (G) determined by ascending electrophoresis, from the valence (m = 6) of the antigen and its total concentration $(G)_o$. The value of p thus found is carried in the expression of (GA) and of (G_2A). From which finally is obtained a value of K for the reaction $G + GA \rightleftharpoons G_2A$.

The results obtained allow to appear a systematic diminution of K at the time when the antigen excess increases (55). The mean value is $(10^4 \pm 4 \times 10^3$ liter/mole for the reaction in veronal buffer at pH 8.5, μ0.1 and 9°C, conditions under which electrophoresis was done. The variation of standard free energy corresponding is -5.4 ± 0.4 Kcal.

The theory of Goldberg presents the advantage of larger coherence over the preceding theories: it does not introduce any irreversible processes, it is valid for all the zones of action of precipitin. It is desirable nevertheless that the repition (REPITION)

be made between the values of equilibrium constants measured in the zone of excess antigen or which can be calculated in the zone of equivalence. It is clear that the equal reactivity of all the groups is an extreme simplification. It is sufficient in order to convince ourselves to conceive of a molecule of ovalbumin already surrounded by 5 molecules of antibody. Moreover, the complete absence of cyclical structure has been without doubt vigorously realized. There can also be nonspecific association established between the molecules of antibody.

Finally, for certain systems we conceive that ~~their~~ these exists differences among the antigenic ~~routes~~ groups or between the two groups of antibody. Kendall(34) has given the example of diphtheria antitoxin, ~~it~~ studied by Pappenheimer and Robinson(45) and by Pappenheimer, Lundgren and Williams(44). The antitoxins appeared to have A_1 and A_2 ~~routes~~ groups of unequal affinity. In treating these groups like the m group G of the toxin as independent molecules, we define an intrinsic constant K_1 corresponding to A_1:

$$K_1 = \frac{(GA_1)}{((A)_0 - (GA_1))\,(m(G)_0 - (GA_1) - (GA_2))}$$

and a similar constant K_2 for equilibrium with A_2. From these constants and the values A_0 and G_0 of the antitoxin and toxin present, we obtain the fraction x and y of groups A_1 and A_2 combined and the number xyA_0 of molecules of antitoxin with which the two groups have reacted. The toxin molecules which are found in the precipitate are those only which are combined with these xyA_0 molecules of antitoxin. We can calculate their number, either by a description of equilibrium equation, or by an application of probability. By choosing for K_1 and K_2 the values ~~xxx~~ 10^8 and 10^4, Kendall has attained excellent agreement with the experimental data.

V. Calarimetric Measurements

A single direct calorimetric measurement has been effected on an antigen antibody system. It has been done by Boyd, Conn, Gregg, Kistiakowsky and Roberts(5). The measurements have been carried out on the hemocyanin of Busycon canaliculatum blood and the corresponding antisera of the horse, in the region of excess antibody,

where no precipitate is formed. In extrapolating the analysis of specific precipitates we obtain for the enthalpy -40 Kcal/mole of antibody. As the reaction proceeds, up to the point of near completion, but where it still can be reversed experimentally, the free energy is estimated at -10 Kcal; it is a consequence of a variation of entropy of -100 Kcal/degree.

There is not a method of research to compare these results with those found, by other methods of approach for other systems. We have seen that the considerable differences are related over again in a series of isohemagglutinins opposite a like agglutinogen. The variations of energy and entropy measured result from a summation of effect and can be interpreted only by comparison between suitably chosen systems.

VI. Conclusions

Resting completely on the limits of established fact, we directly conclude that the thermodynamic study of immunological reaction has already contributed results of great interest. We will say, that, each time a systematic work has been able to be undertaken. Thus the comparison of free energy of combination in a series of haptenes permits first of all, the study of specificity on an atomic scale. The effect of these works supercedes immunochemistry. The same type of experimentation has been extended to the study of enzyme substrate complexes. It can be applied anywhere where one imposes the idea of a complementariness of form in order to give meaning to specificity of action.

From the same comparison of heats of entropy of reaction of isohemagglutinins, there has been discovered on a molecular scale some new facts of general biological interest, for example, the formation of a hybrid protein.

These two categories of research are performed either on the combination of haptene or normal antibody. For reasons which have already been pointed out, the determination of equilibrium constants are simplified in these two cases. But recent progress, theoretical and technical, have led to the opinion that the precipitin reaction will also be the object of measurement in sufficient quantities so that significant results will result.

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Dissertation contents

THERMODYNAMIQUES OF IMMUNOLOGICAL REACTIONS*

By Rene Wurmser, Paris, France

ADV. ENZ. 15:49-77, 1954

mol wt p14

p17

*Translated from French by Roy S. Weinrach

February 28, 1946

Tentative Proposal for Statement.

The scientists who worked on the atomic bomb are at present primarily interested in the possibility of avoiding an atomic arms race. However small the chance might be that this can be successfully accomplished, they are anxious to do nothing that will tend to push us into such an arms race which may lead to a war in which all of our major cities may be destroyed before all avenues have been explored which might lead us away from such a contingency. Primarily it was from this point of view that many of us opposed the passage of the May-Johnson Bill for the control of atomic energy. If our hopes should fail and if we got involved into an atomic arms race, our present manufacturing methods will be very quickly out-dated and we would lose the arms race, if carried on over a five year period, unless we can induce our best scientists to take part in the research and development work on atomic energy. At the present time practically all scientists who were responsible for the success of the atomic bomb have left the Manhattan Project or are in the porcess of leaving. It appears very unlikely that any of them will be willing to work under security regulations similar to those of the May-Johnson Bill--that is, work under conditions under which their telephones are listened to, their letters are opened, reflections cast on their integrity on the ground that they have allowed secrets to leak out, or they may be threatened by prosecution for violations of security rules even though they did nothing more than talk without authorization to other members of the same project. Those who believe that we will be at war within two years need not concern themselves with whether or not the scientists will feel that they can work on atomic energy under some bill similar to the May-Johnson Bill. If war comes within two years, atomic bombs will be made by our present industrial installations and this can be done without the help of any eminent scientists. Those however who fear a long period of international stress rather than an immediate war cannot but be deeply concerned about the danger of controlling atomic energy by some bill which keeps away our best scientists from work on atomic energy.

Expressing ~~Regret~~ Regrets:

~~It is~~ To me it was a matter of profound regret that the Atomic Energy Commission and its General Advisory Board chose this time to provoke a high policy decision on the question of whether or not to develop hydrogen bombs. That such a decision could not be arrived at secretly, and kept secret, was of course a foregone conclusion. A few private persons who had the advantage of advance knowledge were bound to raise their voices. Senators and Congressmen could be expected to have the opportunity of putting in their two bits, and radio commentators could be expected to chime in. But it to the people it is not fair to be confronted with the questions: "Shall we or shall we not build hydrogen bombs?" The large mass of the people are inarticulate, and they cannot be expected to give the right answer to the wrong question.

If, as time went on, the outlines of a possible overall settlement between Russia and the U.S. of the post-war issues had gradually become visible, if there had been some hopeful beginning of successful negotiations with Russia on a broad basis, then we might have been confronted with the issue of choosing between perhaps a not really satisfactory peace settlement and an all-out arms race, including hydrogen bombs, then people, having understood what an all-out arms race would involve and what the proferred post-war settlement would involve, would have had a real choice and might have arrived, for better or for worse, at a reasoned decision.

Inadequacy of Public Discussion:

The question of the hydrogen bomb was sprung on the American public out of a clear sky. This is not the fault of the scientists. The great majority of scientists always believed that the possibilities inherent in the hydrogen bomb ought to be publicly known, for if information of this type is kep secret, public discussion of issues must of necessity be based on false premises. But scientists are not free to use their judgement as to what ought to be and what ought not to be made public. They have to wait until some member of the administration, or some Senator or Congressman mentions something in a speeach, says something over the radio or over TV, or until some one in authority deems it expedient to leak the information to columnists. Then the

scientist heaves a sigh of relief and may attempt to make his views clear in the public discussion which may at that time be already moving fullspeed down the wrong track. In the particular case of the hydrogen bomb, the first public statement was made by John J. McCloy, former Assistant Secretary of War, early in 1946, who related that scientists who worked on the atomic bomb during the war told him that, given two more years of the same effort that went into the making of the bomb during the war, bombs 1000 as powerful as the Nagasaki bomb would be produced. This statement was clear enough, but the scientists were never quite sure whether they would or would not violate the secrecy rules if they disclosed that they believe that the former Assistant Secretary of War was neither a fool not a liar. Things became particularly difficult when Sumner Pike, of the Atomic Energy Commission, gave a speech in which he threw doubt on McCloy's statement by referring to it and pointing out that two years had passed and we still did not have bombs 1000 times as powerful as the Nagasaki one. This rather confused most people, and, because it gave the impression that the statements of McCloy and Sumner Pike could not be reconciled. There is of course no contradiction between these statements, for McCloy prefaced his remarks by saying "given the same intensive effort that went into the making of the bomb during the war," and the last four years certainly did not fulfill these requirements. No more was then heard about the hydrogen bomb in public until it suddenly burst into the columns of various newspapers, who gave information slightly in conflict with each other, but in agreement with each other in the main. Various voices were raised, partly because of inside information, partly because of the information disclosed in the columns, and finally the President's decision was announced.

To the scientists who have lived in their thoughts with ~~the hydrogen bomb~~ it for a number of years, ~~it~~ the hydrogen bomb does not mean what it means to the newspaper reader, who gets his information from reports coming out of Washington in the last few weeks. The Nagasaki bomb was primarily a threat to cities. The action of its blast was demonstrated during the war. It could be used in a more sinister way also, for the production of radio-activity, and since practically all major cities are located near water, and since in many cases the water is none too shallow, a ~~Nagaska~~ Nagasaki type bomb dropped near the city in the water might flood the city with a radio-active spray, and destroy by this method larger areas than it would by blast. But the total amount of radio-activity produced by the Nagasaki type bombs is limited by the amount of plutonium that can be made available for such purposes.

No one has so far exploded a hydrogen bomb, and therefore no one can say for certain that a hydrogen bomb could be made to work, but for the scientists a hydrogen bomb symbolizes unlimited destruction. The amount of radioactivity that can be produced may not be subject to any of the limitations that apply to plutonium bombs. A number of hydrogen bombs rigged for the production of suitable radio-active elements detonated some where west of the American continent could produce enough radio-activity to kill the inhabitants of the U.S. The radio-active elements produced would be carried by the westerly winds accross the continent. By the time they reached the continent of Europe the radio-activity would have dropped to a level which may be tolerated. A number of hydrogen bombs detonated west of the Russian border could sweep Russia. It is not quite easy to adjust the radio-activity in such a manner as to destroy the inhabitants of one continent and by control have it be harmless to the inhabitants of the rest of the world. Nor does a moderate dose that may be spread around the earth and that may not cuase any visible effects to the inhabitants remain necessarily harmless. Above a certain dose no one today

knows what that dose is, a sufficient number of mutations is caused in the population that will remain latent until, through intermarriage during future generations these will gradually begin to manifest themselves in the general deterioration of the human race.

What General Staff entrusted with the sacred duty of winning the war in which it is engaged could we trust to pay due regard to this kind of effect on posterity? Posterity does not represent a threat of revolution to dictators, nor does it have a vote in a democracy.

A country which wishes to put its faith in the hydrogen bomb could, if it is strong minded enough, dispense with all other measures of defense for it can pile up enough hydrogen bombs on its own territory to produce enough radio activity to kill life on the planet. The government may sit back and fold its hands, and in case of agreesion just threaten to detonate its hydrogen bombs, and kill the agressor together with everybody else. This could even be considered as an ideal and cheap way of preserving the peace, if one could only be sure that the agressor would not call the bluff, and if one could be sure that the bluff when called would still remain a bluff, for those in command might feel that freedom is more important than life, and faced with the choice of losing their freedom might prefer to destroy all life. We have not as yet quite reached this stage of madness, but just precisely how far are we from it? A few years ago there was a confidential poll conducted among scientists on a number of issues. One of these concerned the hydrogen bomb. The question was phrased as follows: "Is it in the public interest to develop bombs which are considerably more powerful, or which can be used to create considerable larger amounts of radio activity than the Nagasaki bomb?" A rather impressive majority of those who answered felt that it was not in the public interest to do so. The expression "is it in the public interest?" was

delibertaely chosen to be vague, and there was no attempt made to try to differentiate between the public interest in the pure sense of the term, and the interest of the American people. As a matter of fact, is is doubtful that it is possible from a long range point of view to differentiate between these two.

Naturally among the scientists there are deviations of opinion, and we shall in particular distinguish two main areas which are relevant to the issue, and in which opinions are divided. In order to disentangle what otherwise might lead to a very confused controversy, I shall try first to dispose of the first area of division, whichis important but not fundamental. There are scientists who believe that the possibility of peace with Russia has been adequately explored in the past, that Russia is essentially like Nazi Germany, out to conquer the worlf, that an overall agreement with Russia is not possible, and that the only thing that will deter Russia is a show of force. There are other scientists who do not believe that cooperation with Russia has failed, but are rather inclined to think that it has not been adequately tried. Whether or not such cooperation could be successfully established, if it were adequately tried, hardly anyone ventures to predict. While I myself am inclined to the second view I shall in the following, in order to avoid a blurring of the main issue, adopt for the sake of argument the position taken by the first group, and base all the reasoning on these premises.

Starting from that premise, there is then the abvious and straightforward argument to say that if we don't build hydrogen bombs, and the Russians do, in the absence of any agreement which involves inspection, Russia can force us to surrended by threatening to use hydrogen bombs against us.

If we have hydrogen bombs, so the argument runs, Russia might be deterred from agressive action. Since no one can say with certainty that Russia would in fact be deterred by our possession of hydrogen bombs, it it necessary if we wish to be honest to go one step further and to say expressly that if Russia should attack us in spite of our having hydrogen bombs, we shall use such bombs against her.

Unless we are willing to say so, we have no case.

I believe that most of the scientists who take this line of argument will, upon question, ~~xxx~~ say that if it were merely a matter of a war for one nation against another, they would very much hesitate to go to the lengths of building hydrogen bombs to defend our national existence. But in this view such a war, if it came, would not be fought for the sake of preserving a nation's existence, it would be fought for the preservation of freedom in each. When this point is reached in the discussion, some of those who argue along the above lines will begin to waiver, for they realize that the point has been reached at which we have to re-examine the old values with which we grew up. Before the time of atomic energy a nation was praised for being willing to fight for ~~xxx~~ its freedom to the last man, but in those times the last man meant the last soldier, and the freedom for which he died was the freedom of the civilian who survived. A scientist who is called upon to collaborate in developing a hudrogen bomb is not faced with the ~~q~~uestion of whether he is willing to sacrifice his own life for the freedom of others, but rather whether he is willing to sacrifice other people's ~~xxxxx~~ lives -- masses of civilians, Americans and "foreigners" -- for the preservation of his own freedom. These doubts are much more deep-seated and widespread than is commonly realized, even among those who are inclined to adopt the reasoning described above. And none of those who are beset by such doubts, whether or not they consciously decide to collaborate in the development of hydrogen bombs, will be much good in it, except in as much as their work calls for routine computations rather than ingenuity and originality.

Having outlined one way of reasoning, we now turn to a very different ~~xxxxxxx~~ approach to the general problem. Most scientists, like most people in this country, have no difficulty in agreeing that we cannot trust the Russians. But many of them ask themselves to what extent can we trust ourselves? As long as there is no war the U.S. is one of the most peace-loving countries. Only under

the greatest provocation has the U.S. entered in way with any country. But perhaps just because this country is so peace-loving, whenever it finds itself at war it is very anxious to return as soon as possible to peace. Before the last war American public opinion was unanimous on the issue that warfare against the civilian population of the cities was an abominable atrocity. American reaction to the burning of the Spanish city of Guernica by the Germans and the bombings of London left no doubt where the American people stood on this issue. But when America was at war jellied gas bombs burned and maimed millions of women and children in Japan and it took months before the American people learned about it, and when they did, they pretended not to notice. When the war was already won and with no valid justification, two atomic bombs were dropped on Hiroshima and Nagasaki after a public proclamation naming 12 Japanese cities warning the inhabitants that they would be bombed. The proclaimed list did not contain the names of Hiroshima or Nagasaki. The decision to use the atomic bomb was a governmental decision, but those who lived through those days are very well aware of the fact that this decision would have been upheld by public opinion. The obligations of restraint and moderation that a great power impresses upon a nation were not observed during the last war by the U.S. , and it is not possible to justify these excesses on the grounds that they were necessary to win the war, but they may have been induced by an overwhelming desire to return as fast as possible to conditions of peace. This may or may not be a correct analysis, but the fact is that the atomic scientists were disappointed by this lack of restraint. They know very well that once they develop a weapon they have no appreciable influence on whether or not this weapon will be used. They also know from the experience of the last war that in war time in contrast with other democracies, such as England, the military plays a disproportionately important role in influencing the governmental decisions, and therefore a military point of view will prevail relating to the postwar decisions.

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Proposed Statement - February 27, 1959

Before the last war, little more than ten years ago, Americans regarded the indiscriminate bombing of cities, which inevitably results in casualties among women and children, as reprehensible. American public opinion on this issue was firm, uncompromising, and unanimous. President Roosevelt did no more than give expression to this American public opinion when, in 1939, he warned the belligerents in Europe against resorting to such a method of warfare. When the Germans attacked London with incendiary bombs and high explosives, condemnation of their action in this country was vigorous. The argument that the destruction of London might bring the war to an early end and therefore in the end save lives, both English and German, would not be acceptable as an explanation of what we regarded as an atrocity.

When during the war we began to use jelly gasoline bombs against the citizens of Japan and thus started a type of warfare by means of which we ultimately killed millions of civilians, there was no public announcement by the Administration on what we were about to do; there was no announcement attempting to justify or even explain the kind of warfare which we were about to adopt. And finally, when atomic bombs were available, two of them, that is to say, all we had, were dropped, one over Hiroshima and one over Nagasaki. Thus, before the war we regarded the waging of war against civilians by means of strategic bombing, as the technical term now is, and condemned it as morally wrong, without contesting that it might be expedient, during the war we were lead to engage in this kind of warfare on the ground that it was expedient, without contesting that it might be morally wrong.

In the post war period the Department of Defense, driven by the desire to find a counter-balancing factor to the overwhelmingly strong Russian land forces, has made atomic bombs and strategic bombing in general

the basis of ~~our~~ the defense plans, ~~by~~ which we will guide our actions in case of war. Thus the kind of warfare which we condemned before the war ~~we~~ have now come to regard in peace time as a legitimate method of waging war, ~~if we~~ because it believe that it favors us rather than our potential enemies.

This shift from ~~our~~ the pre war position represents a moral deterioration which is ~~all the more~~ frightening and dangerous because of the rapid rate at which it is still progressing. We cannot very well blame the Germans for this moral deterioration. It is true that Germany started this kind of warfare, but the leaders of Germany were war criminals, who, if caught, were held responsible for their deeds, and tried at Nuremberg. The moral deterioration cannot be blamed on Germany, for the moral standards of a society are determined not by the behaviour of the most abject of its members, but rather by the behaviour of those of its members to whom the others look for moral leadership.

On the occasion of the President's announcement that he had instructed the AEC to develop hydrogen bombs, (an announcement which was not accompanied by an explanation of what hydrogen bombs will mean, why the development is justified, or excusable) -- the growing uneasiness of scientists began to find public expression. This uneasiness is hardly confined to scientists, but scientists, since they are instrumental in developing the weapons, find it more difficult than do other citizens to disclaim responsibility for the military policies and practices adopted by the government.

We consider it our duty at this time to warn the government against continuing on a course which an increasing number of our citizens consider as morally unjustifiable. Wide-spread doubt of the righteousness of our course, whether publicly expressed or not, is the source of dangerous weakness, in a democracy no less than under a dictatorship. ~~In order to remedy a situation which many of us consider intolerable,~~ at this time we wish to make two proposals ~~with~~ which are inter-related. (1) We propose that the ~~U~~ government declare without any further

delay that the U.S. shall not engage in strategic bombing using either atomic bombs or high explosives against any of the countries with who we are allied in the Atlantic Pact, in case any should be occupied by Russia, unless at least as long as the U.S. is attacked by means of atomic bombs which may be manufactured with the borders of the country involved.

2. We propose that the U.S. goverment enter into immediate consultation with the other members of the Atlantic Pact in order to obtain the approval for a declaration by the U.S. to the effect that the U.S. shall not engaged in strategic bombing using either atomic bombs or high explosives against any nation unless that nation first uses strategic bombing against either the U.S. or one of the other Atlantic Pact allies. If

March 2, 1950

When the President announced that he wants America to develop the hydrogen bomb no spokesman of the government explained to the people just what the hydrogen bomb represents.

Yet this is something that the people must know , and this is the reason why I am speaking to you to-day.

What I am going to say to you , any college student majoring in physics, can figure out for himself,oon the basis of published information.

If it becomes possible to détonate practically unlimited amounts of heavy hydrogen , then hydrogen bombs can be used to release very large amounts of radioactive poisons in the air.

I am not speaking here of the radioactivity which a hydrogen bomb will automatically produce in the local area in which it is détonated .

I am rather speaking of the possibility of so rigging the hydrogen bomb as to produce a much larger amount of radioactive poisons in the moment of its explosion.

These poisons would be released in the air and would be carried and dispersed by the winds.

It would take a ~~comparatively small~~ number of ~~rather~~ large bombs to kill , within the course of a few years every human being on earth through radiactive dust which would be generated at the moment of explosion and which would gradually settle everywhere.

There might be some doubt whether the inhabitants of the southern hemisphere might survive while the inhabitants of the northern hemisphere perish if the bombs are detonated in the northern hemisphere and the bombs are not too large or numerous.

Perhaps some of you will say that all this is just fine.

Instead of spending many billions for defense, for the army, the navy and the airforce, we can now save all this expense , which is a growing burden on our economy, and incidentally a burden which might sky rocket in the next few years to twenty five, thirty or even thirt y five billion dollars.

All we now have to do is to build up such bombs, and let the world know that if any conqueror reaches our shores, our bombs and release radioactive poisons which will , in a few years at the most, will kill them along with killing ourselves.

Even though, from the financial point of view , this might be a far cheaper way of safeguarding our security than any other hitherto devised , I cannot say that I am entirely happy about it.

For When the fate of the world hangs on the sanity of the Commander in Chief, or the Secretary of Defense, or the Chief of staffs, the fate of the world hangs on a thin thread.

You may ask "can't we just spread radioactive poisons into the air enough to kill all the Russians or can the Russians not kill us all by this method without danger to themselves ?"

It would certainly take much fewer bombs or much smaller bombs

to produce radioactive ~~poisons~~ dust enough to cover either the area of Russia or the area of America , ~~sufficiently densely~~ and to kill all the inhabitants.

But the problem is to get this ~~poison~~ dust into the area where ~~we~~ you want it and to keep it away from the area where you dont want it , ~~and~~ I am happy to ~~say that~~ I do not know whether this problem is favorable at all , and I sort of suspect that no one at present knows whether it can be ~~solved~~ known favorable.

For the time being it is therefore permissble to hope that this ~~problem~~ not favorable is insoluble, though I ~~am afraid we cannot~~ would not be too sure of it.

What I am saying to you here, I am not saying in order to scare you , I am saying it to you because I believe that you must know it even though it might scare some of you.

I am one of those who have not given up faith in the possibility of reaching an overall settlement with Russia .

I believe that we must try to do that , and if we fail we must try it again , and if we fail again, we must again try it until at last we may succeed.

To those ~~who~~ of you who have lost faith in the possibility of ~~avoiding~~ averting war, a war which may come five, ten, fifteen or twenty years hence, I have only one consolation to offer :

I can say , as another speaker on atomis bombs said before me, there situation is serious , perhaps ~~it is hopeless~~ , but this is nothing to get excited about ; after all, it is not as if the earth were a major planet.

March 17, 1950

Since it is difficult to qualify remarks of this sort in the Round Table discussion, I wish to take this opportunity to set forth the following:

If it becomes possible to detonate heavy hydrogen by suddenly heating up a sufficiently large amount to a sufficiently high temperature so that as to set up a self propogating thermo-nuclear reaction, then we will have created a situation which, for the first time in history, the finite size of the earth as becoming significant. It would then be possible for the United States for instance, to build up a fairly small number of very large bombs and to rig them so as to produce radioactive substances which would be disbursed in the air and which would gradually settle as a dust all over the world. To make this bomb so large as to produce enough radioactive substances to kill everyone on the Northern Hemisphere or even everywhere on the Earth would require a large industrial enterprise, but one which is entirely within the realm of feasibility. The United States could then make known that rather than suffer invasion or bombardment of our cities from the air by an enemy, it would detonate these bombs and kill the whole population of the enemy as well as her own population. The United States would be invincible providing only that she succeeded in persuading the enemy that the threat would in fact be carried out.

The initial investment required for ~~this type of~~ defense based on suicide bombs would be substantial, but once it is made, no further appreciable defence expenditure would needed to be incurred in contrast with the present situation which in the course of ten years our defence expenditure might skyrocket from 15 to 25, 35, or even 45 billion dollars?

The trouble is, of course, that the decision to detonate the suicide bombs in a given contingency could hardly be left to democratic processes if the enemy is to take the threat seriously. This decision ~~will of necessity~~ have to be placed in the hands of ~~some tightly knit organization or even be intrusted to a single man;~~ the Commander in Chief or the Secretary of Defense, or the Chief of Staff. When the fate of the world hangs on the decision of a single man or a small group of men, the fate of the world hangs on a thin thread, for no single man is immune from insanity in the ~~medical~~ sense of the ~~word~~ and no small group of men is immune from insanity in the broader sense of the term.

The initial investment required is determined both by the number of bombs and the amount of heavy hydrogen contained in the individual bombs. Because the detonator of the bomb require substantial quantities of elements which are expensive to obtain--as has been pointed out by H. Thirring in 1946--it is of advantage to keep the number of bombs to a minimum and rather to use whenever possible large individual bombs. For the particular application ~~which is discussed here,~~ it is not necessary to have the bombs transported and even though there are reasons why more than one bomb should be used, it is difficult to see that any appreciable advantage would be gained by increasing the number of bombs above 50. The ~~exact~~ total amount of heavy hydrogen needed ~~even though it may not be the prime factor of cost if~~ 50 bombs are used can be estimated on the following basis:

1. ~~If~~ one ton of neutrons is absorbed by ~~neutral~~ element which is incorporated in the bomb, ~~and if~~ each neutron gives rise to one radioactive atom which upon decaying emits a gamma ray of 1 million volts of energy, ~~and if~~ the radioactive

substance produced settles uniformly as a dust on the surface of the Earth. ~~A~~ man standing on the surface of the Earth and exposed to ~~the~~ gamma radiation will receive a dose of x-ray units during which the radioactive substance decays. A dose of about ~~1 thousand R~~ given within a period of a month or so may be considered as lethal. ~~This dose would then correspond to so many tons of neutrons.~~ If the dose is given not over a period of months but several years, a ten times larger dose would be required to produce a lethal effect. This data is somewhat uncertain, but all we are considering here are orders of magnitude. ~~[illegible]~~ 1000 R units would thus require about 50 tons of neutrons i.e. of the order of magnitude of 100 tons of neutrons "usefully" absorbed could be lethal ~~for the worker~~ man. In the first step of the decision in which two things happens

1 part in 5000

1000 tons of Heavy Hydrogen

500 × 5000 tons of ordinary hydrogen

25 million tons of Hydrogen

15 million Tons of Coal

$H_2O + C \quad H_2 + CO$

for 10,000 tons of Heavy Hydrogen

150 million Tons of Coal

Article

March 20, 1950

In the first step of the reaction in which two heavy hydrogen atoms react with each other, about half of the reaction will lead to a neutron being emitted while the other half will lead to the emmission of a proton. Thus about ten tons of heavy hydrogen would have to be burned in this manner in order to produce one ton of neutrons. The subsequent reactions might increase the number of neutrons liberated. Not all the neutrons emitted in the explosion can be captured in the natural element which may be incorporated in the bomb nor need necessarily all the heavy hydrogen present in the bomb be burned in the explosion. Taking these things into consideration one might guess that the total amount of heavy hydrogen contained in the bombs necessary to produce the desired effect might be somewhere between 500 tons and 5,000 tons. A closer estimate might perhaps be given but to do so would be neither easy nor permissible. Clearly the number of neutrons which can be usefully captured will depend on the absolute shape and measurements of the bomb and the fraction of the heavy hydrogen which ~~wixx~~ is actually burned in the bomb as well as the degree to which it is burned depends on the number of details.

Insert

In order to burn any amount of heavy hydrogen, small or large, we must ~~set~~ initiate the process by setting up a nuclear reaction, and this requires appreciable quantities of substances which are difficult to obtain and which are therefore correspondingly expensive (see, for instance, Thirring). The cost of this nuclear detonator is of little importance if very large amounts of heavy hydrogen can be ~~detonated~~ "burned" in one bomb. But if the amount of hydrogen that can be burned in a bomb is small, then the ~~relative~~ cost of the detonator is ~~appreciable.~~ the controlling factor.

March 20, 1950

The only naturally occurring light element suspected of being explosive is heavy hydrogen. For many years now, physicists have been pursued by the nightmare that it might be possible to detonate heavy hydrogen. If it is in fact possible to set up a thermal nuclear reaction in heavy hydrogen (by suddenly heating up a sufficiently large quantity of heavy hydrogen to sufficiently high temperatures) and thus to "burn" in any one bomb an amount of heavy hydrogen which is unlimited in principle ~~(and is limited in practice only be the stockpiles of heavy hydrogen which have been accumulated or by considerations of expediency)~~ then we might stand on the threshold of a new epoch in the history of mankind.

~~Whether hydrogen bombs can in fact be~~ Because the President has ~~stated that he has~~ instructed the Atomic Energy Commission to proceed with the development of the hydorgen bomb, it is now generally assumed that ~~our experts must believe~~ there is a reasonable chance that ~~heavy hydrogen can in fact be detonated.~~

If these experts should prove to be wrong, it might still perhaps be possible to burn limited amounts of heavy hydrogen in an atomic explosion ~~in which, as has been pointed out, substantial amounts of either plutonium or Uranium 235 would be used for setting off the bomb.~~ Such an abortive development of the hydrogen bomb, while perhaps ~~not entirely without~~ some military interest would hardly be of general interest ~~and will therefore be disregarded in the discussion of our topic.~~

Assuming then that heavy hydrogen can be detonated, the total amount of heavy hydrogen that a country like the United States or Russia might make available over a period of ten years for this purpose could be very large indeed. ~~This country could accumulate without any substantial strain on their economy say 10,000 pounds in a period of ten years, and since~~ there would be no limit on the raw materials ~~required~~ which are essentially water and coal even though the initial investment would be quite substantial. There might be some limitation ~~on the raw material side~~ on the number of bombs that either of these countries could make since each bomb will require a substantial

quantity of plutonium or Uranium 235 (see Theiring). Because of the possibility of such limitations, let us assume that the total quantity of such hydrogen bombs will be about 100, and that we devided 10,000 pounds of heavy hydrogen over these 100 bombs so that each one of them contains about 100 tons of heavy hydrogen. Such bombs might then be too big to deliver by air to targets in enemy territory and as a matter of fact there hardly exists any targets that would require such very large bombs.

The question then may be asked, is there any use for such large bombs which are no longer transportable? It appears likely that the United States and Russia might make themselves invincible in the course of the next ten or fifteen years by accumulating such a initial quantity of heavy hydrogen in a comparatively small number of bombs.

There might very well be such a use and as a matter of fact, it appears possible that either the United States or Russia might make themselves invincible in the course of the next ten or fifteen years by accumulating such a large quantity of heavy hydrogen in a comparatively small number of bombs.

In order to understand this, we have to point out that this possibility is based on the following facts. A very large number of neutrons are liberated in the moment of explosion of a hydrogen bomb is detonated. Most natural elements are formed into a radio active element if they absorb neutrons and by incorporating a suitable natural element into the hydrogen bomb so as to permit it to absorb the neutrons liberated in the moment of explosion, very large quantities of radio active substances can be produced. If the hydrogen bomb is so rigged as to produce a long-lived radio active element and if the radio active substances which are produced in the explosion are permitted to rise in the atomosphere, they will be generally dispersed by winds and gradually reach the upper part of the atmosphere everywhere, just as did the dust from the Cractoa eruption. If the Cractoa pattern is followed

this dust would settle down in the course of one or two years covering the crust of the earth fairly uniformly in a thin layer. People everywhere then would be exposed to the ~~apparent~~ penetrating radiation of this dust and in the course of a few years, recieve a radio active dose which is lethal.

If the United States, for instance, built a sufficient number of such bombs and would let the world know that rather than allow the bombing of her cities or invasion, if necessary she would detonate her suicide bombs, killing all the population of ~~her~~ the enemy together with her own population. The United States would be invincible provided only that she can persuade the enemy that the threat will in fact be carried out.

From the financial point of view, this method of defense, in spite of the initial expenditure involved, might well represent a considerable easing of ~~her~~ the economic burden. For in the next ten or fifteen years our expenditures for the army, navy, air forces, and civilian defense might very well sky rocket from 15 to 25, 35, or even 45 billion dollars per year.

Nevertheless it is difficult to get enthusiastic about this ~~comparatively inexpensive~~ method of defense for clearly in order to make the threat effective it would be necessary to place the decision of detonating these bombs in the hands of a small group of people if not a single man. Any single man might be inflicted with insanity in the narrow sense of the word, and any group of men might be inflicted with insanity in the broader sense of the word. Thus when the fate of the world will hang on the sanity of a few men, the fate of the world will hand on a thinn thread.

Yet, it must be said that defense by suicide bombs is by no means the most repugnant form of radio active warfare that might become possible. In an article written three years ago, Professor Edward Teller described a different method of radio active warfare which is far more repulsive and which, through not envisaging suicide, might nevertheless prove to be not less suicidal. Dr. Teller's article appears in the Bulletin of the Atomic Scientists, pages 35-36, Volume III, February, 1947, and was cleared prior to publication with the Atomic Energy Commission. Dr. Teller wrote:

"In a subject as new as atomic power, we must be prepared for startling developments. It has been repeatedly stated that future bombs may easily surpas those used in the last war by a factor of a thousand. I share this belief...The radioactivity produced by the Bikini bombs was detected within about one week in the United States. In the meantime the westerly winds had swept the air mass from Bikini to this country...If the activity liberated at Bikini were multiplied by a factor of a hundred thousand or a million, and if it were to be released off our Pacific Coast, the whole of the United States would be endangered. That the enormous amounts of activity just mentioned can in actuality be released at some future date is by no means an established fact; but it is much more than a fantastic possibility. If such great quantities of activity should become available, an enemy could make life hard or even impossible for us without delivering a single bomb into our territory. ... It is to be noted that different radioactive products have different rates of decay. The attacker is therefore in a position to choose the radio active products best suited to his attack; with the proper choice he could ensure that his victim would be seriously damaged by them and that they would have decayed by the time they reached his own country. Naturally this is not easy, but under the circumstances, within the realm of possibility."

The possibility of the type of radio active warfare described by Teller hinges on the outset on a number of questions which are not as yet available to the public and which are probably known to no one. As the radio active substances produced in the explosion is allowed to escape high in the stratosphere, it might travel several times around the earth and decay without harming anyone before it will appear in the atmosphere from where it might effect the population. Can the bulk of the radio active substances be prevented from rising to the stratosphere without having the bulk of the radio active substances percipitating out in a spotty manner unsuited to the type of warfare described by Teller. All these are difficult questions to answer. The one factor which favors this method of warfare though, is the fact that the amount of radio active substances that would have to be generated and the individual effort that would be required to produce that amount of heavy hydorgen would be very much smaller than in the case of the defense based on "murder and suicide" bombs.

The radio active warfare which Teller describes, if it is feasible, may prove to be just as suicidal as the defense based on murder and suicde for presumably, what we can do to our enemy, our enemy can do to us. And with prevailing secrecy the increasing tendency of overestimating ourselves and underestimating our enemies, the radio active warfare that two nations plan against each other might easily turn out a pos tiori as suicide even though it was planned only as murder.

For a man who is exposed to gamma radiation given within a short period of time, a dose of 1,000 r may be assumed to be lethal. If the dose is given over a period of years, a larger dose is needed to kill, just precisely how much is not known. For the purposes of this discussion, it is assumed that a dose of the order of magnitude of 10,000 r is lethal if given over a period of years. If a number of hydrogen bombs are exploded and of the neutrons liberated, 50 tons are in toto absorbed in cobalt so that they

produce radio active cobalt and if this radio active cobalt is uniformly dispursed over the surface of the earth a man exposed to the gamma radiation of this dust would in toto receive a dose of the order of 10,000 r by the time the cobalt decays. Fifty tons of [illegible] neutrons correspond to 500 tons of heavy hydrogen actually burned in the explosion. Since not all neutrons produced in the explosion will actually be absorbed in the cobalt incorporated in the bombs, and since not all the heavy hydrogen in the bombs will actually be burned, and since moreover a somewhat larger dose might be necessary to kill, particularly since if it will be made to remove the cobalt dust from the surface of the earth, we have in estimating the economic effort involved assumed the accumulation of 10,000 rather than of 500 tons of heavy hydrogen, by the beligerant who wants to base his defense of murder and suicide. We are not particularly concerned at this time with trying to decide whether or not this type of defense is in fact practicable and we have gone into such details only in order to demonstrate that we are now rapidly approaching a stage of development when the limiting ~~of~~ the earth beomes relevant and the method of resolving conflicts by relying on superior strength that will permit a nation if necessary to fight a victorious war will not longer be applicable. This development which started with the demonstration of atomic bombs at the end of the last war has been going on ever since and as it progresses it shifts the basis on which a reasonable foreign policy ~~has been~~ based.

In the absence of an overall agreement between America and Russia and even in the absence of an agreement dealing with disarmament in general, if an agreement is limited to atomic energy then international management of atomic energy has the advantage of permitting to get by without introducing general measures of inspection or opening up other chanels of obtaining information in general. In 1945, it was probably true that international management of

atomic energy would have given us very good safeguards against evasion of the agreement and perhaps an international management was not even necessary for that purpose. For in 1945, Russia had no bombs and even if Russia had managed to divert some plutonium or Uranium 235 from its legitimate uses into clandestine channels, she could hardly have tested an atomic bomb without our discovering it seeing that we have in fact discovered the first Russian bomb test without any measures of inspection.

Today it seems that it is very unlikely that international control of atomic energy will be acceptable either to Russia or America except if it is accompanied by far reaching measures of general disarmament and it is equally unlikely that far reaching measures of general disarmament will be acceptable without an overall agreement which appears to have a reasonable degree of stability. However, if the agreement extends beyond the control of atomic energy into the general field of all armaments, and if it is considered equally important to control long range rockets, long range bombers, and long range submarines, as it is to control the raw materials of atomic bombs, then the acceptance of international management in the field of atomic energy will no longer have the advantage of permitting us to get by without opening up new channels of general information. That Russia will be reluctant to expose herself to inspection and espionage will be taken for granted and in the present conditions she may h ve valid reasons for this reluctance. It will therefore be necessary to examine under what conditions Russia would cease to h ve such valid reasons and can such conditions be created.

If such conditions can be created, then the issue of international management and perhaps even the issue of inspection in the narrow sense of the term will lose its importance. It is not likely that any of the make shift measures proposed for the international control of atomic energy and disarmament would offer us sufficient safeguards under conditions of a

cold war. The state in which e ought to be interested is the state of what you may call total peace, and if we can't have total peace, an issue that will be examined later, the technical problems of inspection disappear. In total peace there is no legitimate reason for maintaining an espionage accound or an official secret account and with the legal protection for secrecy gone, spying become a legitimate and honorable profession. When the stage is reached that an overall settlement has been aggred upon and the technical issue arises ~~xxx~~ how either Russia or the United State can learn whether the agreement is adhered to, what Russia and the United States ought to insist on is the right to maintain spies and the immunity of spies from persecution. Without some such immunity there can be no safety.

In 1945 it was probably correct to think that international management of atomic energy had great advantages over other methods of control schemes for as long as one thinks of an agreement that is limited to this particular field and which does not cover the general field of armaments, international management would permit us to get by with a minimum amount of general inspection. At a time, however, when it is rather obvious that we must think of control of atomic energy as part of an overall settlement to which Russia and America might be a party, international management of atomic energy can hardly any longer appear as a particularly att active possibility. In place of trying to approach the problem of establishing durable peace by thinking of approaching such a peace by piecemeal agreements, we ought rather to look at the problem with which we are faced by starting from the other end, that is we have to ask ourselves what would an agreement-adjusted total peace involve and having arrived at an answer, see how the particular problem of atomic energy control would fit into its overall framework. In thinking about the solution of this problem, it is necessary first of all to agree on certain premises.

1.) While peace after the First World War could very well have been based on collective security, the principle of collective security is not adequate for the preservation of peace in the situation which has now arisen. Because of the mechanism of war, only those countries are and will be important military powers which can have a wide margin between their total production and total consumption. This margin is wide for the United States because the production capacity of the United States far exceeds its comsumption needs. This margin is large for Russia because the people in Russia are accustomed to and willing to take a low standard of living. With the possible exception of a united Germany, there is no other nation which this would hold true for the foreseeable future, and therefore Russia and America are today and will remain in the forseeable future, powers that cannot be coerced by collective action short of war, nor could collective action by war against either of them lead to a forseeable period of time to victory.

Once this is recognized, it is clear that if we can have an overall settlement between Russia and America at all, it ~~can be enforced~~ will remain in force only if it does not run counter at any time to the vital interests of America and Russia and if ~~continuous~~ understandings will be maintained in the world in which it remains in the continued interest of Russia and America to maintain the agreement in force. Moreover, in the ~~xxxxxxxxxx~~ condition which exists today, it is very difficult to conceive of any international body to which both countries could rely trust the right to adjudicate grievances which might arise out of the implementation of the agreement. It is therefore logical to think that the United States and Russia should ~~render~~ retain the right legally to abrogate in self defense if they feel their vital interests are threatened because the agreement is not properly implemented. The right to abrogate is the only weapon which Russia and the United States would ~~render~~ have that would enable them effectly to press for a remedy of a complaint arising out of the implementation of the agreement. The right to abrogate ~~has~~ is, of course, ~~naturally limitations in fact which will be discussed later, but it covers such areas as atomic energy disarmament and such other topics which are today considered to fall within the conception of national sovereignty.~~ limited to areas such as control of atomic energy, which are considered at present to be within the realm of national sovereignty. Because of ~~the~~ overall distrust, rivalry, and those elements of the power conflict which cannot be entirely eliminated from the period of the cold war, it would be advisable to rely as the sole force of working toward maintaining the agreement on the fear of the consequences of the resumption of the arms race which would follow an abrogation. It will rather be necessary to create conditions in which the agreement is maintained ~~in~~ not so much by the fear of the consequences of abrogation as rather by the economic and social ~~collective~~ cultural insentives which a continuation of an agreement offers.

This letter is addressed to seventeen American scientists to whom it will be communicated two weeks after its appearance in print. Because of their scientific achievement, these men have the respect of the community of scientists which extends beyond the confines of the United States. Moreover each one of them has shown in the past ~~that he is~~ willing to take action outside of the narrow field of his profession if this is demanded by the public interest. The names have been selected with a view to obtaining a balanced group which is broadly representative of the thinking of scientists in America.

To the Secretary of State
Washington, D. C.

Letter of Transmittal

September 5, 1950

I have the honor of transmitting to you a copy of a letter which will be sent to a number of scientists whose names are listed in the enclosure. Because of their scientific achievement, the names of these men are known beyond the confines of the United States, and each one of them has shown in the past that he is willing to take action outside of the narrow field of his profession if this is required by the public interest. I believe that Hans J. Morganthau, of the Department of Political Science at the University of Chicago, has express what many scientists feel when he wrote in the May issue of the Bulletin of the Atomic Scientists as follows:

"...I do not know whether a negotiated settlement with the Soviet Union is possible. I do know, however, that no such attempt at a negotiated settlement has been made; instead we have wasted our time with polemics over isolated secondary issues which must remain insoluble as long as the basic issues remain unsettled. I also know that, in view of the present and foreseeable distribution of power between the United States and the Soviet Union, the choice before the world is between negotiated settlement and war, that is, universal destruction. I finally know that no nation can survive the ordeal of a third world war, if it can survive it at all, without being convinced in its collective conscience that it has done everything humanly possible to preserve peace. It is for these reasons that I deem it worth while and even imperative to consider seriously the possibility of a negotiated settlement with the Soviet Union."

What is the proper time to start negotiations with Russia aimed at comprehensive settlement?

Wilkie was of the opinion that the proper time for negotiating a settlement with Russia was during the war, before Russia and America lost their common enemy. Many of us believe that he was right and that if reaching a satisfactory agreement with Russia is possible at all, with every year that is allowed to elapse it will be more and more difficult. much are.

Copy of memorandum by

The State Department's position with respect to this issue has been made public through the statement which you issued to the press on February 8 and your Berkeley speech on March 16. The State Department appears to think that as time goes on our strength in certain important areas of the world will increase and with it will increase our chance to reach a satisfactory over-all settlement with Russia. In the meantime, according to the State Department, all we are asking is that Russia behave; all the Russians have to do is abide by the United Nations Charter and all will be well; all the American people have to do is be patient and stand firm.

I know very few scientists to whom this makes any sense.

Suppose the Russians do behave and suppose they do abide by the United Nation's Charter, there is nothing in the Charter from preventing them from building up enormous strength in atomic weapons and to developing means of delivering atomic bombs first to any point in Western Europe and later to the coastal cities of the United States. By doing so, the Russians would only follow the example which we have been setting them.

Yet this will inevitably have the result that more and more Americans will think in terms of preventative war. Not a preventative war right now perhaps, but rather a "show down" when we shall be good and ready. More and more men in high positions in our government will be thinking in these terms and even if they do not make any public statements their views will not remain a secret for long; and whatever everybody in Washington knows, the Russians may be assumed to know also. Can we, in these circumstances, expect the Russians to behave and to wait until we are good and ready? The policy of the State Department is based on the premise that it is possible over a long period of time to go on without an over-all settlement and in the meantime hold the line and build up our strength. In my opinion, this premise is false. The American people cannot be expected to be patient and firm, and the State Department cannot be expected to exercise control over the public utterances of high officials in the Department of Defense, much less so about their thinking, and cannot whatever over the reactions of the Russians.

In my opinion this premise is false. The American people cannot be expected to be patient and firm. The State Department is not able to control the public utterances of high official of the Department of Defense and even less to guide their private thoughts which are just as important as their public utterances. The Russians will respond to every one of our actions, whether it is a decision of making H-bombs or any other measure undertaken for the purpose of strengthening our military position with some action of their own. The State Department cannot be expected to see their "encounter" in advance. It will be necessary to improvise and one single mistake will be enough to bring on war.

I do not mean to say that the government of the United States ought to enter into negotiations with Russia at this time. It is doubtful whether such negotiations could produce any useful result if they were entered into without a clear concept as to precisely what would constitute a satisfactory settlement that might bring up durable peace; it is no reason to believe that the State Department has a clear concept of this and in any case the almost complete absence in the past of any public discussion of the issue would make the task of the State Department very difficult.

A group of outstanding American citizens, free from any governmental responsibility and devoting their full time from three to six months to this task might think through the problems involved and might emerge with a plan which in their opinion ought to be acceptable both to Russia and America. It is however, difficult for American citizens to take into account all the points of view which might legitimately enter into the considerations of the Russian government. The danger of overlooking an important point would be therefore greatly diminished if the group engaged in such study were composed of both Russians and Americans, without in any way courting either of the two governments. ~~it is this consideration which the letter addressed to my colleagues which you will find enclosed is based on this consideration.~~

4

Perhaps the only way of finding out what kind of an over-all settlement might be a real possibility is to have an exchange of views between Americans and Russians. And because an exchange of views is useful only if views are exchanged between men who have mutual respect for each other's intellectual integrity, [the plan outlined in the enclosure would appear at this time to be a ~~much~~ more promising venture than ~~it~~ would actual negotiations between the two governments.]

Many believed that he was right, and that if it is at all possible to reach a satisfactory agreement with Russia, it becomes more difficult with every year that is allowed to elapse.

and that in reaching an agreement with Russia is at all possible, it becomes more difficult with every year that is allowed to pass.

To the Secretary of State
Washington D.C.

September 6, 1950

Sir:

I have the honor of transmitting to you a copy of a letter which will be sent to seventeen American scientists whose names are listed in the enclosure.

I believe that Hans J. Morgenthau, of the Department of Political Science at the University of Chicago, has expressed what many scientists feel when he wrote in the May issue of the Bulletin of the Atomic Scientists as follows: "...I do not know whether a negotiated settlement with the Soviet Union is possible. I do know, however, that no such attempt at a negotiated settlement has been made; instead we have wasted our time with polemics over isolated secondary issues which must remain insoluble as long as the basic issues remain unsettled. I also know that, in view of the present and foreseeable distribution of power between the United States and the Soviet Union, the choice before the world is between negotiated settlement and war, that is, universal destruction. I finally know that no nation can survive the ordeal of a third world war, if it can survive it at all, without being convinced in its collective conscience that it has done everything humanly possible to preserve peace. It is for these reasons that I deem it worth while and even imperative to consider seriously the possibility of a negotiated settlement with the Soviet Union."

What is the proper time to start negotiations with Russia aimed at a comprehensive settlement? Wilkie was of the opinion that the proper time for negotiating a settlement with Russia was during the war, before Russia and America lost their common enemy. Many of us believe that he was right and that if reaching a satisfactory agreement with Russia is possible at all, with every year that is allowed to elapse it will be more difficult to reach

There would be no point in urging the State Department to push into relations with Russia at this time. It is doubtful whether such negotiations

I do not mean to say that the government of the United States ought to enter into negotiations with Russia at this time. It is doubtful whether such negotiations could produce any useful result if they were entered into without a clear concept of just what would constitute a satisfactory settlement. There is no evidence to show that the State Department has a clear concept of this and in any case the absence of any public discussion of the issues would make the task of the State Department very difficult.

To outline a satisfactory settlement that might be acceptable both to Russia and America as well as to all other nations involved, is clearly a difficult task. For a settlement to be satisfactory it would have to create conditions which would induce both America and Russia to maintain the agreement in operation over a long period of time. Such an agreement would have to include general measures of disarmament, which are far-reaching in scope, and provide adequate safeguards against violations. While Russia and America might retain under such an agreement the right legally to abrogate the disarmament clauses of the agreement, a number of other nations would have to be bound by the agreement as long as the agreement is not legally abrogated, and, therefore, the creation of some machinery of enforcement might be deemed to be necessary.

There are no doubt men on your staff who think it is impossible to devise a satisfactory agreement along such lines or any other lines which Russia could conceivably accept. These men may prove to be right. But just because they are not able to devise such an agreement it does not mean that such an agreement may not be devised if we succeed in enclisting the help of men who have shown themselves to be resourceful in other fields and whose imagination is left unshackled.

October 17, 1950

Dean Acheson gave a clear exposition of the foreign policy of the United States in the statement which he issued to the press on February 8. Since that day there can be no doubt what our foreign policy is. We are not going to seek an over-all settlement with Russia, but we are going to try to create situations of strength in a number of different areas, and having created such a situation, we are going to attempt to perpetuate it by getting Russians formally to recognize it. Of all the areas involved, the most important is Europe, and it seems to be now generally recognized in the United States that it will be possible to create such a situation of strength in Western Europe without rearming Germany to make Western Europe a reliable stronghold. It might take full-scale rearmament of Germany both because of the great industrial potential of Germany and because Germany has a nation is more military than France, we will probably as time goes on rely more and more on Germany and less and less on France for the defense of Western Europe. A Germany rearmed cannot be a nation without a will of its own. The obvious national aims of Germany must be representative of what party is in power after Germany has recovered the territory which she lost to Poland. Thus the Germans have something to fight for much more than do the French, and if so once they can be expected to carry their own burden. If Russia is defeated, we can hardly expect American to police that enormous country, but the Germans can be relied on to do this. Thus the end result of the war if we somewhat optimistically there will be a short war over in a few years there will be a short war over in a few years will be a situation which we could have had for the asking in 1939 without having to pay Second World wars for it. In order to creat a situation of strength in Western Europe, we have embarked on a remarmament program on a scale involved in spending $300 million dollars per year, and we plan to maintain a standing army of three million men. As far as manpower is concerned, such an army cannot be maintained on our "income", for a draft of the 18 year olds is insufficient to fit it and it will be necessary, of course, for us to dig into our manpower capital since it doesn't

appear likely at all. Even if you assume that the United States can afford both from the economic point of view and from the point of view of its manpower a perpetual preparedness, it appears doubtful that the people of the United States will reconcile themselves to such a state of affairs. It is therefore not astonishing that more and more people will talk privately of the possibility of a preventative war and that some of these men like Mr. Matthews, Secretary of the Navy, will talk publicly about it. The State Department, of course, frowns on such public utterances, and I believe is sincere in doing so. The trouble, however, is that our actions make sense on the assumption that we are going to war within a few short years and that they make no sense unless this is what we intend to do. The State Department may, of course, think that the present policy of creating situations of strength need not be pushed through to the bitter end and that somewhere before then we will have created enough strength to have Russia sign on the dotted line, but no one who really understands the situation as it exists today in the world and who is able to think through to the consequences of this appraoch can believe that the method attempted can lead to the establishment of real peace. If we had to deal here with the negotiations between two private parties, one might very well say that a party who is in the strong position when it comes to concluding an agreement will be able to obtain a more favorable agreement. This makes sense because once an agreement is signed it cannot be abrogated since an agreement between private parties can be brought into court and the party who violates it can be if not forced to keep the agreement at least be held financially responsible for the damage. It is likely that we will have within the forseeable period a situation in the world where a treaty between the United States and Russia can be enforced. It seems likely that after the first world war a system of collective security could have been established and would have prevented the outbreak of the Second World War. But in these last 30 years, the situation has changed materially in this respect because war has become so highly mechanized. Only those few countries can respect an appreciable

who can have a large margin between their nation's production and national consumption which can be left over for war production. The United States is in this class because its high production standard permits a high standard of living and yet leaves a sufficient margin for war production. Russia is such in this category because its people are willing to except a low standard of living that a substantial margin is left for war production. It might be a reconstituted Germany in the grips of a strong natio and with its manufacturing facilities reconstructed may also fall into this category and so might Japan. But that's the end of it. It is clear that no system of collective security can be built in this situation upon which the world could rely to enforce a str obligation either against Russia or against the United States. It follows, therefore, that an over-all settlement between the United States and Germany will be of value only

October 18, 1950

Dean Acheson gave a clear exposition of the foreign policy of the United States in a statement which he issued to the press on February 8. This statement leaves no doubt whatsoever as to what his foreign policy is. He is not going to seek an over-all settlement with Russia but intends to try to create situations of strength in a number of different areas and having created such situations attempt to perpetuate them by getting Russia formally to recognize them.

When this statement of policy was issued, it was not as clear what the pursuit of the policy would involve as it is today.

Today it seems to be generally recognized in the United States that it will not be possible to create such a situation of strength in Western Europe--the most important of all the areas involved--without rearming Germany. In order to make Western Europe militarily secure to the point where we can rely on Western Europe as a base of military operations in case of war, full scale rearmament of Germany will probably be necessary. Because Germany has a nation is more militant than is France, it is likely that astime goes on, we will rely more and more on Germany and less and less on France for the defense of Western Europe.

A Germany rearmed cannot be a nation without a will of its own. A Germany united and with its territories that were taken by Poland restored are legitimate aims of national aspiration on which all Germans, irrespective of party, can be expected to be united. The Germans will have something to fight for much more so than the French and once their industries are reconstructed, they can be expected to carry their own burden.

If we disregard the possibility that the world war will be on before a fully militarily reconstructed Germany has taken over the main burden of the defense of Western Europe, and if we somewhat optimistically assume that the war will come after Western Europe has become militarily secure, that it will last just a few years, and that we shall be victorious, American may be relieved of the burdensome task of policing Russia by leaving it to Germany to do so. On the basis of a series of optimistic assumptions, we can thus look forward to a state of affairs in Europe which we could have had for the asking in 1939 without

having to fight two world wars for the sake of getting it.

The trouble with this kind of thinking is that it tries to apply the remedies of the past to the ills of the present. It is probably true that collective security could have prevented the second world war had the principle of collective security been understood and supported by the people of the United States in 1919. But it is not true that the problem which the world faces today can be solved on the basis of organizing a system of collective security of building up a situation of strength that will induce Russia to agree to some over-all settlement which is favorable to us and then rely on collective security for the enforcement of that treaty. Clearly if enforcing a treaty may require a world war which may last for twenty or thirty years and the outcome of which is uncertain, using the term of enforcement is either misleading or deceiving. And clearly if an over-all settlement which is signed among others by the United States and Russia is illegally abrogated either by the United States or Russia, ~~no enforcement short of such a world war~~ there is no possibility of enforcing compliance with the treaty short of such a world war which the treaty was intended to prevent. It is not likely that this situation should cange within one generation or two. For the change which came in the methods of warfare since the first world war have made the principle of collective security impractical. What has happened since the first world war is that mechanization of armies reached a level which makes it impossible for most countries to maintain or create an armed force that is militarily significant compared with the armed forces of the United States and Russia. A possible exception ought to be made perhaps for a reconstructed and remilitarized Germany. Clearly because of the high level of mechanization, maintaining armed forces of a significant strength has become exceedinly expensive and only those countries can afford such armed forces which have a great margin between their industrial production and their civilian comsumption. The United States has a large margin because it is so rich, and Russia has a large margin because the standard of living of its cililian population can be kept low. A reconstructed and remilitarized Germany might have a fairly large margin because Germany has

always been a militant nation and because the German people once they awaken from their present lethargy are likely to accept a low standard of living in exchange for a chance of achieving their national aspirations; a united Germany and the recovery of their territories lost in the last war. No other nation is likely to have an appreciable margin between its consumption and civilian production in the next twenty-five years. And the organization of a system of collective security upon which the world could rely for the enforcement of a peace settlement either against the United States or against Russia is therefoer impossible. It should be observed that if a peace settlement cannot be enforced it can be obtained over a long period of time only if both Russia and the United States consider it in their interest to keep the agreement in force. In these circumstances, one might as well give Russia and the United States the right legally to abrogate the agreement upon due notice and the insertion of such a clause into the agreement might serve the purpose of reminding the atatesmen that the task of preserving peace is tantamount to maintaining peace in the world in which it is not the continued interest of the United States and Russia to maintain the agreement in operation. If this point of view is accepted, then clearly the task which we are facing is to devise an agreement which is so well adjusted to the vital needs of Russia and the United States--vital needs in which peace and prosperity are certainly a major part for both countries, that Russia and the United States will maintain the agreement in force even if they have the right legally to abrogate it because the agreement continues to meet their requirements so that each year they would conclude it anew if perchance the agreement contained a time limit and should therefore lapse. If this analysis of the situation is correct, then it can hardly serve vital purposes for Russia and the United States to build up strength in order to exhort from one another an advantagous agreement, since clearly the problem is not to obtain an agreement which these nations are willing to sign but rather an agreement which these nations are anxious to keep. These two problems are very different in nature and if it

should happen that the over-all negotiations take place when over-all opposition seems to be very strong, it would be exceedingly foolish to use this strnegth in order to get Russia to sign an agreement which she will no longer want to keep later when our position may happen to be less strong. If these considerations are valid, then it is clearxx that our foreign policy makes no sense at all and the only remaining question is whether it is at all possible to devise an agreement that will meet the stringent requirements defined above.